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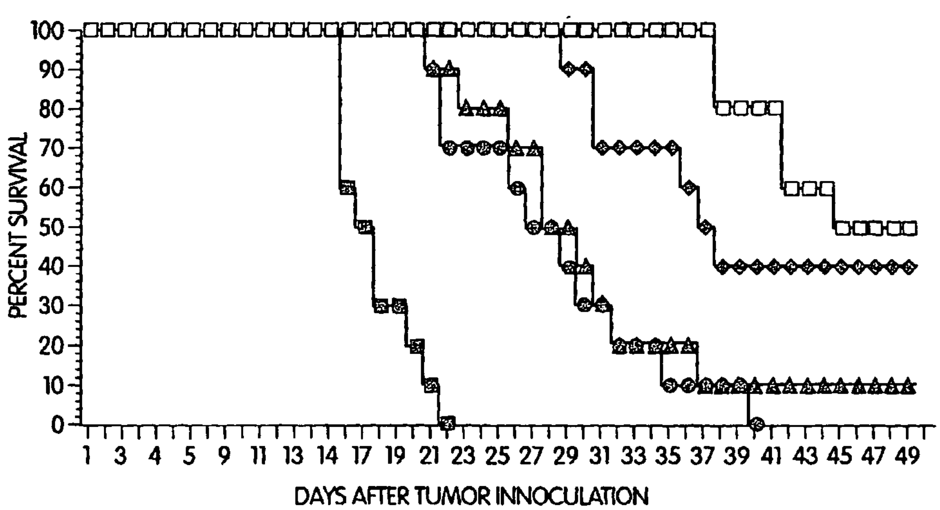
(54) Title: METHODS FOR ENHANCING ANTIBODY-INDUCED CELL LYSIS AND TREATING CANCER



(57) Abstract: The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibobdies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

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METHODS FOR ENHANCING ANTIBODY-INDUCED CELL LYSIS AND TREATING CANCER

PRIORITY

This application claims the benefit of U.S. Provisional Application No. 60/213,346, filed June 22, 2000.

FIELD OF THE INVENTION

The invention relates to the treatment and prevention of cancer using immunostimulatory nucleic acids and antibodies.

BACKGROUND OF THE INVENTION

Cancer is the second leading cause of death, resulting in one out of every four deaths in the United States. In 1997, the estimated total number of new diagnoses for lung, breast, prostate, colorectal and ovarian cancer was approximately two million. Due to the ever increasing aging population in the United States, it is reasonable to expect that rates of cancer incidence will continue to grow.

Cancer is a disease which involves the uncontrolled growth (i.e., division) of cells. Some of the known mechanisms which contribute to the uncontrolled proliferation of cancer cells include growth factor independence, failure to detect genomic mutation, and inappropriate cell signaling. The ability of cancer cells to ignore normal growth controls may result in an increased rate of proliferation. Although the causes of cancer have not been firmly established, there are some factors known to contribute, or at least predispose a subject, to cancer. Such factors include particular genetic mutations (e.g., BRCA gene mutation for breast cancer, APC for colon cancer), exposure to suspected cancer-causing agents, or carcinogens (e.g., asbestos, UV radiation) and familial disposition for particular cancers such as breast cancer.

Cancer is currently treated using a variety of modalities including surgery, radiation therapy and chemotherapy. The choice of treatment modality will depend upon the type, location and dissemination of the cancer. For example, surgery and radiation therapy may be more appropriate in the case of solid well-defined tumor masses and less practical in the case of non-solid tumor cancers such as leukemia and lymphoma. One of the advantages of

surgery and radiation therapy is the ability to control to some extent the impact of the therapy, and thus to limit the toxicity to normal tissues in the body. However, surgery and radiation therapy are often followed by chemotherapy to guard against any remaining or radio-resistant cancer cells. Chemotherapy is also the most appropriate treatment for disseminated cancers such as leukemia and lymphoma as well as metastases.

More recently, the use of CpG containing nucleic acids has been proposed for the treatment and prevention of cancer. We have found that unmethylated CG-dinucleotides within certain sequence contexts (CpG DNA) are recognized by the vertebrate immune system as foreign DNA (bacterial or viral). CpG DNA activates a coordinated set of immune responses that include innate immunity (macrophages, dendritic cells, and natural killer cells), humoral immunity, and cellular immunity. Krieg AM et al., *Pharmacol Ther* 84:113-20 (1999); Krieg AM et al., *Curr Top Microbiol Immunol* 247:1-21 (2000); Wagner H, *Adv Immunol* 73:329-68 (1999). As a vaccine adjuvant, CpG DNA is at least as effective as the gold standard complete Freund's adjuvant (CFA), but induces higher Th1 activity and demonstrates less toxicity. Chu RS et al., *J Exp Med* 186:1623-31 (1997); Weiner GJ et al., *Proc Natl Acad Sci USA* 94:10833-7 (1997); Roman M et al., *Nat Med* 3:849-54 (1997); Lipford GB et al., *Eur J Immunol* 27:2340-4 (1997); Davis HL et al., *J Immunol* 160:870-6 (1998). Recently, we identified a human CpG motif which triggers proliferation and activation of primary human B cells. Hartmann G et al., *J Immunol* 164:944-53 (2000).

SUMMARY OF THE INVENTION

The invention relates in some aspects to methods for treating and preventing cancer using immunostimulatory nucleic acids and antibodies. Thus in one aspect the invention is a method for treating or preventing cancer. The method involves administering to a subject having or at risk of developing cancer an effective amount to upregulate CD20 expression of a nucleic acid, and an anti-CD20 antibody. The cancer, in some embodiments, is B-cell lymphoma associated with low levels of CD20 expression. The B-cell lymphoma in other embodiments is B-cell chronic lymphocytic leukemia (B-CLL) or a marginal zone lymphoma. In some embodiments the CD20 antibody is C2B8 or Rituximab.

The invention in other aspects relates to a method for diagnosing lymphoma by isolating a B cell from a subject and identifying a change in cell surface markers when the B cell is contacted with an immunostimulatory nucleic acid, wherein the cell surface marker

induced on the B cell is indicative of the type of lymphoma. In some embodiments the subject has a type of lymphoma. In some embodiments the subject is suspected of having a type of lymphoma. The method may optionally include a method for treating cancer by administering to the subject an immunostimulatory nucleic acid and an antibody specific for the cell surface antigens induced on the B cell in order to treat the cancer.

In another aspect the invention is a method for treating or preventing cancer by administering to a subject having or at risk of developing cancer an effective amount to induce expression of a surface antigen on a cancer cell surface, of a nucleic acid, and administering to the subject an antibody selected from the group consisting of an anti-CD22 antibody and an anti-CD19 antibody.

According to another aspect of the invention, a method for treating lymphoma is provided. The method includes the steps of isolating a B cell from a subject having lymphoma, identifying a surface antigen which is not expressed or which is expressed on the surface of the B cell in an amount lower than that of a control B cell, administering to the subject an antibody specific for the identified surface antigen and an immunostimulatory nucleic acid in order to treat the lymphoma, wherein the nucleic acid is administered in an effective amount to upregulate expression of the surface antigen on the lymphoma cell surface.

A method for treating a lymphoma resistant to antibody therapy is provided according to another aspect of the invention. The method includes administering to a subject having a lymphoma resistant to therapy with an antibody specific for a surface antigen, an antibody specific for the surface antigen to which the lymphoma is resistant and a nucleic acid in order to treat the lymphoma, wherein the nucleic acid is administered in an effective amount to upregulate expression of the surface antigen on the lymphoma cell surface.

The surface antigen may be any type of surface antigen which is capable of being expressed on the surface of a cancer cell and which is induced by stimulation with immunostimulatory nucleic acids. In some embodiments the surface antigen is CD20, CD40, CD22, or CD19. In other embodiments the lymphoma is B-CLL or marginal zone lymphoma. In some embodiments the antibody is an anti-CD20 antibody. In some embodiments the anti-CD20 antibody is C2B8. In another embodiment the anti-CD20 antibody is Rituximab.

In some preferred embodiments the antibody is a human IgG1 antibody. In some preferred embodiments the antibody is a murine IgG2a antibody.

In some embodiments the methods also include administering an anti-cancer therapy to the subject.

The invention also includes a method for treating cancer in a human by administering to a human an immunostimulatory nucleic acid and an antibody of IgG1 isotype (an IgG1 isotype antibody as used herein refers to a human or humanized IgG1 unless otherwise specified), which binds to a cell surface antigen of a cancer cell and wherein the nucleic acid and the antibody are administered in an effective amount for killing the cancer cell.

Optionally the nucleic acid and the antibody are administered together. Alternatively the nucleic acid and the antibody may be administered separately.

In some embodiments the method includes the step of administering a cancer therapy. As used herein the term "a cancer therapy" is meant to embrace a single medicament, a plurality of medicaments of a particular class and a plurality of medicaments of different classes, and includes but is not limited to chemotherapeutic agents, cancer vaccines, biological response modifiers, and hormone therapies.

A chemotherapeutic agent may be selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, non-sugar containing chloroethylnitrosoureas, 5-fluorouracil, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, fragyline, Meglamine GLA, valrubicin, carmustaine and poliferposan, MMI270, BAY 12-9566, RAS famesyl transferase inhibitor, famesyl transferase inhibitor, MMP, MTA/LY231514, LY264618/Lometexol, Glamolec, CI-994, TNP-470, Hycamtin/Topotecan, PKC412, Valspodar/PSC833, Novantrone/Mitroxantrone, Metaret/Suramin, Batimastat, E7070, BCH-4556, CS-682, 9-AC, AG3340, AG3433, Incel/VX-710, VX-853, ZD0101, ISI641, ODN 698, TA 2516/Marmistat, BB2516/Marmistat, CDP 845, D2163, PD183805, DX8951f, Lemonal DP 2202, FK 317, Picibanil/OK-432, AD 32/Valrubicin, Metastron/strontium derivative, Temodal/Temozolomide, Evacet/liposomal doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, Xeload/Capecitabine, Furtulon/Doxifluridine, Cyclopax/oral paclitaxel, Oral Taxoid, SPU-077/Cisplatin, HMR 1275/Flavopiridol, CP-358 (774)/EGFR, CP-609 (754)/RAS oncogene inhibitor, BMS-182751/oral platinum, UFT(Tegafur/Uracil), Ergamisol/Levamisole, Eniluracil/776C85/5FU enhancer, Campto/Levamisole, Camptosar/Irinotecan, Tumodex/Ralitrexed, Leustatin/Cladribine, Paxex/Paclitaxel,

Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, ZD1839, LU 79553/Bis-Naphtalimide, LU 103793/Dolastain, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, ZD 0473/Anormed, YM 116, Iodine seeds, CDK4 and CDK2 inhibitors, PARP inhibitors, D4809/Dexifosamide, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, ZD 9331, Taxotere/Docetaxel, prodrug of guanine arabinoside, Taxane Analog, nitrosoureas, alkylating agents such as Melphalan, Cyclophosphamide, Aminoglutethimide, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Dactinomycin, Daunorubicin HCl, Estramustine phosphate sodium, Etoposide (VP16-213), Floxuridine, Fluorouracil (5-FU), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Leuprolide acetate (LHRH-releasing factor analogue), Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mesna, Mitotane (o,p′-DDD), Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Amsacrine (m-AMSA), Azacitidine, Erythropoietin, Hexamethylmelamine (HMM), Interleukin 2, Mitoguazone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG), Pentostatin (2'deoxycoformycin), Semustine (methyl-CCNU), Teniposide (VM-26) and Vindesine sulfate.

In some preferred embodiments the chemotherapeutic agent may be selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, valrubicin, Novantrone/Mitroxantrone, Evacet/liposomal doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, SPU-077/Cisplatin, HMR 1275/Flavopiridol, BMS-182751/oral platinum, Leustatin/Cladribine, Paxex/Paclitaxel, Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, Taxotere/Docetaxel, prodrug of guanine arabinoside, nitrosoureas, alkylating agents such as melphalan and cyclophosphamide, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Daunorubicin HCl, Etoposide (VP16-213), Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mitoxantrone HCl, Procarbazine HCl, Thioguanine, Thiotepa, Vinblastine sulfate,

Azacitidine, Interleukin 2, Pentostatin (2'deoxycoformycin), Teniposide (VM-26), GM-CSF, and Vindesine sulfate.

A cancer vaccine may be selected from the group consisting of EGF, Anti-idiotypic cancer vaccines, Gp75 antigen, GMK melanoma vaccine, MGV ganglioside conjugate vaccine, Her2/neu, Ovarex, M-Vax, O-Vax, L-Vax, STn-KHL theratope, BLP25 (MUC-1), liposomal idiotypic vaccine, Melacine, peptide antigen vaccines, toxin/antigen vaccines, MVA-based vaccine, PACIS, BCG vaccine, TA-HPV, TA-CIN, DISC-virus and ImmuCyst/TheraCys. Biological response modifiers include interferon, and lymphokines such as IL-2. Hormone replacement therapy includes tamoxifen alone or in combination with progesterone. In a further embodiment, the cancer therapy is interferon-α (e.g., INTRON® A, Schering).

The cancer may be selected from the group consisting of basal cell carcinoma, bladder cancer, bone cancer, brain and central nervous system (CNS) cancer, breast cancer, cervical cancer, colon and rectum cancer, connective tissue cancer, esophageal cancer, eye cancer, kidney cancer, larynx cancer, leukemia, liver cancer, lung cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, melanoma, myeloma, oral cavity cancer (e.g., lip, tongue, mouth, and pharynx), ovarian cancer, pancreatic cancer, prostate cancer, rhabdomyosarcoma, skin cancer, stomach cancer, testicular cancer, and uterine cancer. In preferred embodiments, the cancer to be treated may be selected from the group consisting of bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer (e.g., lip, tongue, mouth, and pharynx), skin cancer, and testicular cancer.

In another aspect the invention encompasses a kit. The kit includes a package including at least two containers, the first container housing an immunostimulatory nucleic acid, the second container housing an antibody specific for a cell surface antigen, and instructions for screening a cell to determine whether the immunostimulatory nucleic acid upregulates expression of the cell surface antigen. In one embodiment the antibody is selected from the group consisting of an anti-CD20 antibody, an anti-CD19 antibody, and an anti-CD22 antibody.

The nucleic acids useful according to the invention are immunostimulatory nucleic acids and in some embodiments are immunostimulatory CpG nucleic acids having an

unmethylated CpG motif, immunostimulatory T-rich nucleic acids, immunostimulatory poly-G nucleic acids, bacterial DNA, yeast DNA, or eukaryotic DNA.

In some embodiments the nucleic acid does not hybridize with genomic DNA or RNA under stringent conditions. In other embodiments the nucleic acid does hybridize with genomic DNA or RNA under stringent conditions.

The nucleic acid may have natural linkages or may include at least one modified backbone internucleotide linkage. In some embodiments the modified backbone is a phosphate backbone modification. In other embodiments the modified backbone is a peptide modified oligonucleotide backbone. The nucleic acid may also include native bases or modified bases. The nucleotide backbone may be chimeric, or the nucleotide backbone is entirely modified.

The immunostimulatory nucleic acid can have any length greater than 6 nucleotides, but in some embodiments is between 8 and 100 nucleotide residues in length. In other embodiments the nucleic acid comprises at least 20 nucleotides, at least 24 nucleotides, at least 27, nucleotides, or at least 30 nucleotides. The nucleic acid may be single-stranded or double-stranded. In some embodiments the nucleic acid is isolated and in other embodiments the nucleic acid may be a synthetic nucleic acid.

The CpG nucleic acid in one embodiment contains at least one unmethylated CpG dinucleotide having a sequence including at least the following formula: 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, wherein X_1, X_2, X_3, and X_4 are nucleotides. In one embodiment the 5' $X_1X_2CGX_3X_4$ 3' sequence of the CpG nucleic acid is a non-palindromic sequence, and in other embodiments it is a palindromic sequence.

In some embodiments X_1X_2 are nucleotides selected from the group consisting of: GpT, GpG, GpA, ApA, ApT, ApG, CpT, CpA, CpG, TpA, TpT, and TpG; and X_3X_4 are nucleotides selected from the group consisting of: TpT, CpT, ApT, TpG, ApG, CpG, TpC, ApC, CpC, TpA, ApA, and CpA. In other embodiments X_1X_2 are GpA or GpT and X_3X_4 are TpT. In yet other embodiments X_1 or X_2 or both are purines and X_3 or X_4 or both are pyrimidines or X_1X_2 are GpA and X_3 or X_4 or both are pyrimidines. In one embodiment X_2 is a T and X_3 is a pyrimidine.

In other embodiments the CpG nucleic acid has a sequence selected from the group consisting of SEQ ID NOs: 19, 35-37, 39-42, 91, 92, 101, 108, 111, 135, 141, 151, 274, 277, 280, 286, 319, 350, 363, 368, 375, 495-498, 517, 518, 524, 529, 545, 548, 549, 555, 557,

560-563, 566, 585, 590, 591, 595, 599, 603, 605, 611, 614-616, 650, 676, 679, 682, 684, 702, 703, 707-710, 717-720, 729-732, 752, 755, 770, and 801-803.

In some embodiments the T-rich immunostimulatory nucleic acid is a poly-T nucleic acid comprising 5' TTTT 3'. In yet other embodiments the poly-T nucleic acid comprises 5' $X_1X_2TTTTX_3X_4$ 3' wherein X_1, X_2, X_3, and X_4 are nucleotides. In some embodiments X_1X_2 is TT and/or X_3X_4 is TT. In other embodiments X_1X_2 is selected from the group consisting of TA, TG, TC, AT, AA, AG, AC, CT, CC, CA, CG, GT, GG, GA, and GC; and/or X_3X_4 is selected from the group consisting of TA, TG, TC, AT, AA, AG, AC, CT, CC, CA, CG, GT, GG, GA, and GC.

The T-rich immunostimulatory nucleic acid may have only a single poly-T motif or it may have a plurality of poly-T nucleic acid motifs. In some embodiments the T-rich immunostimulatory nucleic acid comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 T motifs. In other embodiments it comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 CpG motifs. In some embodiments the plurality of CpG motifs and poly-T motifs are interspersed.

In yet other embodiments at least one of the plurality of poly-T motifs comprises at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, or at least 9 contiguous T nucleotide residues. In other embodiments the plurality of poly-T motifs is at least 3 motifs and wherein at least 3 motifs each comprises at least 3 contiguous T nucleotide residues or the plurality of poly-T motifs is at least 4 motifs and wherein the at least 4 motifs each comprises at least 3 contiguous T nucleotide residues.

The T-rich immunostimulatory nucleic acid may include one or more CpG motifs. In other embodiments the T-rich immunostimulatory nucleic acid is free of one or more CpG dinucleotides.

In other embodiments the T-rich immunostimulatory nucleic acid has poly A, poly-G, and/or poly C motifs. In other embodiments the T-rich immunostimulatory nucleic acid is free of two poly C sequences of at least 3 contiguous C nucleotide residues. Preferably the T-rich immunostimulatory nucleic acid is free of two poly A sequences of at least 3 contiguous A nucleotide residues. In other embodiments the T-rich immunostimulatory nucleic acid comprises a nucleotide composition of greater than 25% C or greater than 25% A. In yet other embodiments the T-rich immunostimulatory nucleic acid is free of poly-C sequences, poly-G sequences or poly-A sequences.

In some cases the T-rich immunostimulatory nucleic acid may be free of poly-T motifs, but rather, comprises a nucleotide composition of greater than 25% T. In other embodiments the T-rich immunostimulatory nucleic acid may have poly-T motifs and also comprise a nucleotide composition of greater than 25% T. In some embodiments the T-rich immunostimulatory nucleic acid comprises a nucleotide composition of greater than 25% T, greater than 30% T, greater than 40% T, greater than 50% T, greater than 60% T, greater than 80% T, or greater than 90% T nucleotide residues.

In some embodiments the poly-G nucleic acid comprises: 5' $X_1X_2GGGX_3X_4$ 3' wherein X_1, X_2, X_3, and X_4 are nucleotides. In embodiments at least one of X_3 and X_4 are a G or both of X_3 and X_4 are a G. In other embodiments the poly-G nucleic acid comprises the following formula: 5' GGGNGGG 3' wherein N represents between 0 and 20 nucleotides. In yet other embodiments the poly-G nucleic acid comprises the following formula: 5' GGGNGGGNGGG 3' wherein N represents between 0 and 20 nucleotides.

The poly-G immunostimulatory nucleic acid may include one or more CpG motifs or T-rich motifs. In other embodiments the poly-G nucleic acid is free of one or more CpG dinucleotides or poly-T motifs.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts data from flow cytometry which demonstrates the induction of a morphologic change in marginal zone lymphoma cells upon CpG oligonucleotide stimulation. Malignant B cells from a patient with marginal zone lymphoma were stimulated with no oligonucleotide (A and D), control oligonucleotide (ODN 2017, SEQ ID NO: 168, B and E) or CpG oligonucleotide (ODN 2006, SEQ ID NO: 729, C and F) and analyzed by flow cytometry. A, B, and C illustrate forward scatter (FSC; x-axis) vs. side scatter (SSC; y-axis). D, E and F illustrate CD19 expression (x-axis) against FSC (y-axis).

Figure 2 depicts data from flow cytometry which demonstrates the change in expression of surface antigens on marginal zone lymphoma cells upon CpG oligodoexynucleotide (ODN) treatment. Flow cytometric analysis of surface antigen expression on malignant B cells from a patient with marginal zone lymphoma was performed

using either CpG or non-CpG oligonucleotide. Thin curves indicate incubation with medium alone, dotted curves indicate incubation with control oligonucleotide, and bold curves indicate incubation with CpG oligonucleotide.

Figure 3 is a set of bar graphs depicting changes in expression of surface antigens on primary cells representing different B-cell malignancies and cells of a benign follicular hyperplasia upon treatment with, from left to right in each panel: negative control, no oligonucleotide, control oligonucleotide (ODN 2017, SEQ ID NO: 168), or CpG oligonucleotide (ODN 2006, SEQ ID NO: 729). Each panel represents one experiment.

Figure 4 is a set of graphs depicting the observation that the effect of CpG oligonucleotide on CD20 (top) and CD40 (bottom) is dependent on the baseline level of expression of CD20 and CD40. Cells from lymph node biopsies, peripheral blood or pleural fluid from patients with different B-cell malignancies were incubated with or without CpG oligonucleotide, and expression of CD20 and CD40 was measured by flow cytometry.

Figure 5 depicts data from flow cytometry which demonstrates the effect of CpG oligonucleotide-induced proliferation of malignant and normal B cells. Peripheral blood mononuclear cells from patients with B-CLL (left) or marginal zone lymphoma with circulating malignant cells (right), were incubated with CpG oligonucleotide (bottom) or medium alone (top) and evaluated by two-color flow cytometry. CFSE fluorescence (x-axis) and expression of CD5 (B-CLL) or CD19 (marginal zone lymphoma) (y-axis) were evaluated.

Figure 6 is a graph depicting the survival of mice injected on Day 0 with tumor cells in response to CpG simulation in combination with murine IgG2a and murine IgG1 anti-tumor antibodies. Treatments are shown as filled squares, untreated controls; filled circles, murine IgG1; filled triangles, murine IgG1 plus CpG; filled diamonds, murine IgG2a; and open squares, murine IgG2a plus CpG.

DETAILED DESCRIPTION

Present cancer treatments are often ineffective as well as being associated with a high degree of patient morbidity. The invention provides methods and products for the more effective treatment of cancer using a combination of immunostimulatory nucleic acids, antibodies, and optionally cancer therapies.

The invention is based, in part, on the surprising discovery that administration to a subject of immunostimulatory nucleic acids induces the expression of cell surface antigens including CD20, CD19, and CD22 on the surface of a cancer cell and that the induction of these antigens leads to enhanced antibody-dependent cellular cytotoxicity (ADCC). It was previously believed that CpG oligonucleotides enhanced ADCC by influencing the effector cell (e.g., by activating natural killer (NK) cells). Now it has been discovered according to the invention that immunostimulatory nucleic acids actually cause the induction of specific antigens CD20, CD19, and CD22, each of which can be targeted by specific antibody therapies. The discovery that immunostimulatory nucleic acids are capable of upregulating expression of certain target antigens on the surface of cancer cells, supports the development of therapies using immunostimulatory nucleic acids in combination with specific antibodies which interact with these cell surface antigens. Thus, in one aspect, the invention provides a method for treating or preventing cancer which involves the administration to a subject of a combination of an immunostimulatory nucleic acid and an antibody which specifically interacts with CD20, CD19, and CD22 in an effective amount to prevent or treat the cancer.

Additionally, it was discovered that the increased expression of these and other cell surface antigens varies widely depending upon the histological state of the tumor cell studied. The effect of immunostimulatory nucleic acids on different types of primary malignant B cells and reactive follicular hyperplasia was extensively examined. All B-cell lymphoma cells tested increased in size and granularity, upregulated activation markers (CD80, CD86, CD40, CD54, CD69), and upregulated antigen presentation molecules (class I major histocompatibility complex (MHC I), class II major histocompatibilty complex (MHC II)) in response to immunostimulatory nucleic acids. A control poly-C oligodeoxynucleotide (ODN) showed only minor effects. The extent of phenotypic change induced by immunostimulatory nucleic acids differed from sample to sample. Immunostimulatory nucleic acids, but not control nucleic acids, increased the expression of co-stimulatory molecules (e.g., CD40, CD80, CD86, CD54) on malignant B cells without altering the phenotype of B cells derived from reactive follicular hyperplasia. Immunostimulatory nucleic acids also enhanced expression of both class I and class II MHC in most samples. CD20 expression was increased in response to immunostimulatory nucleic acids, most notably in B-CLL and marginal zone lymphoma.

Furthermore, an inverse correlation was found between baseline expression of specific cell surface antigens and their expression after exposure to immunostimulatory nucleic acids. Thus the most significant increase in expression of these molecules was found in those samples that had the lowest (or no) baseline levels. These data indicate that immunostimulatory nucleic acids may reverse low expression of co-stimulatory molecules on malignant B cells that correspond to a low level of activation, while their effects on cells that are already in an activated state are less profound.

Thus, the invention relates to methods for identifying an appropriate therapy for a lymphoma patient, and for treating the patient using that therapy. The method can be accomplished by isolating a B cell from a lymphoma patient and comparing the surface antigens expressed on the malignant B cell with those expressed on normal B cells. The antigens which are expressed in low levels or not at all on the malignant B cell can be identified. The subject can then be treated using a combination of an immunostimulating nucleic acid and an antibody which specifically recognizes the antigen(s) which are expressed in low levels or not at all on the malignant B cell.

The invention is also useful for treating cancers which are resistant to monoclonal antibody therapy. It has been discovered according to the invention, that immunostimulatory nucleic acids can reverse the resistance of tumor cells and render tumor cells which were previously non-responsive or only weakly responsive, sensitive to therapy. In particular it has been discovered that immunostimulatory nucleic acids can cause a phenotypic change to a resistant tumor cell that renders it sensitive to monoclonal antibody therapy. For instance, the monoclonal anti-CD20 antibody Rituximab has been shown to be effective clinically in several trials and has recently been approved for the therapy of follicular B cell lymphoma. Maloney DG, *Semin Oncol* 26:74-8 (1999); Foran JM et al., *J Clin Oncol* 18:317-24 (2000); Witzig TE et al., *J Clin Oncol* 17:3793-803 (1999); Davis TA et al., *J Clin Oncol* 17:1851-7 (1999); Wiseman GA et al., *Clin Cancer Res* 5:3281s-3286s (1999); Grillo-Lopez AJ et al, *Semin Oncol* 26:66-73 (1999). There are reports that with lymphomas a small minority of tumors that re-emerge following Rituximab therapy can lack CD20 expression. Davis TA et al., *Clin Cancer Res* 5:611-5 (1999); Kinoshita T et al., *J Clin Oncol* 16:3916 (1998). The immunostimulatory nucleic acids of the invention are useful for treating this set of resistant tumors. Additionally, Rituximab has not been useful for the treatment of all types of B cell malignancies. Expression of CD20 is relatively low on B-CLL cells, which provides an

explanation for why Rituximab is less effective for CLL than for some other B-cell malignancies. Grinaldi L et al., *J Clin Pathol* 51:364-9 (1998). The immunostimulatory nucleic acids of the invention are also useful for treating these tumors.

The humanized monoclonal antibody 1D10 recognizes an HLA-DR variant antigen. Link BK et al., *Blood* 81:3343-9 (1993). This antibody is currently being tested in a phase I clinical trial in patients with lymphoma. One limitation to the use of this antibody is that the target antigen is only expressed by approximately 50% of B-cell lymphomas. Interestingly, its expression was upregulated by immunostimulatory nucleic acids in all lymphoma samples tested. It was discovered according to the invention that immunostimulatory nucleic acids may enhance the efficacy of therapy with these and other antibodies by increasing expression of target antigen. Thus in another aspect the invention includes methods for treating lymphoma by administering to a subject an immunostimulatory nucleic acid and antibodies specific for HLA-DR. One useful antibody is the humanized monoclonal antibody 1D10. It is particularly useful for treating resistant tumors.

The invention also relates to the discovery of a specific subclass, or isotype, of antibody which when combined with immunostimulatory nucleic acids produces a synergistic immune response. Another subclass, or isotype, does not even provide an additive response when combined with immunostimulatory nucleic acids. It was discovered according to the invention that the combination of immunostimulatory nucleic acids and human antibodies of the IgG1 isotype results in an increased (synergistic) survival rate. When immunostimulatory nucleic acids are combined with human antibodies of the IgG2 isotype, no increase in survival rate is observed over the use of the IgG2 antibody alone. The IgG2 isotype (which correlates with the murine IgG1 isotype) is believed to be recognized by the Fc receptor designated CD16 that is expressed largely by NK cells. Immunostimulatory nucleic acids are known to activate NK cells, and thus, it is surprising that immunostimulatory nucleic acids do not enhance the therapeutic effect of human IgG2 or murine IgG1 antibodies. Since NK cells are believed to be involved in ADCC and are activated by immunostimulatory nucleic acids, it was surprising that antibodies of the human IgG2 (or murine IgG1) isotype do not produce a synergistic or even additive response when administered with immunostimulatory nucleic acids.

A cancer cell is a cell that divides and reproduces abnormally due to a loss of normal growth control. Cancer cells almost always arise from at least one genetic mutation. In some

instances, it is possible to distinguish cancer cells from their normal counterparts based on profiles of expressed genes and proteins, as well as to the level of their expression. Genes commonly affected in cancer cells include oncogenes, such as ras, neu/HER2/erbB, myb, myc and abl, as well as tumor suppressor genes such as p53, Rb, DCC, RET and WT. Cancer-related mutations in some of these genes leads to a decrease in their expression or a complete deletion. In others, mutations cause an increase in expression or the expression of an activated variant of the normal counterpart.

The term "tumor" is usually equated with neoplasm, which literally means "new growth" and is used interchangeably with "cancer." A "neoplastic disorder" is any disorder associated with cell proliferation, specifically with a neoplasm. A "neoplasm" is an abnormal mass of tissue that persists and proliferates after withdrawal of the carcinogenic factor that initiated its appearance. There are two types of neoplasms, benign and malignant. Nearly all benign tumors are encapsulated and are noninvasive; in contrast, malignant tumors are almost never encapsulated but invade adjacent tissue by infiltrative destructive growth. This infiltrative growth can be followed by tumor cells implanting at sites discontinuous with the original tumor. The method of the invention can be used to treat neoplastic disorders in humans, including but not limited to: sarcoma, carcinoma, fibroma, glioma, leukemia, lymphoma, melanoma, myeloma, neuroblastoma, retinoblastoma, and rhabdomyosarcoma, as well as each of the other tumors described herein.

"Cancer" as used herein refers to an uncontrolled growth of cells which interferes with the normal functioning of the bodily organs and systems. Cancers which migrate from their original location and seed vital organs can eventually lead to the death of the subject through the functional deterioration of the affected organs. Hemopoietic cancers, such as leukemia, are able to out-compete the normal hemopoietic compartments in a subject, thereby leading to hemopoietic failure (in the form of anemia, thrombocytopenia and neutropenia), ultimately causing death.

A metastasis is a region of cancer cells, distinct from the primary tumor location, resulting from the dissemination of cancer cells from the primary tumor to other parts of the body. At the time of diagnosis of the primary tumor mass, the subject may be monitored for the presence of metastases. Metastases are most often detected through the sole or combined use of magnetic resonance imaging (MRI) scans, computed tomography (CT) scans, blood

and platelet counts, liver function studies, chest X-rays and bone scans in addition to the monitoring of specific symptoms.

Cancers include, but are not limited to, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and CNS cancer; breast cancer; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; kidney cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g., small cell and non-small cell); lymphoma including Hodgkin's and non-Hodgkin's lymphoma; melanoma; myeloma; neuroblastoma; oral cavity cancer (e.g., lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; renal cancer; cancer of the respiratory system; sarcoma; skin cancer; stomach cancer; testicular cancer; thyroid cancer; uterine cancer; cancer of the urinary system, as well as other carcinomas and sarcomas.

The immunostimulatory nucleic acids and antibodies are useful for treating or preventing cancer in a subject. A "subject" unless otherwise specified shall mean a human or vertebrate mammal including but not limited to a dog, cat, horse, cow, pig, sheep, goat, or primate, e.g., monkey. Thus the invention can be used to treat cancer and tumors in human and non human subjects. Cancer is one of the leading causes of death in companion animals (i.e., cats and dogs). Cancer usually strikes older animals which, in the case of house pets, have become integrated into the family. Forty-five percent of dogs older than 10 years of age are likely to succumb to the disease. The most common treatment options include surgery, chemotherapy and radiation therapy. Other treatment modalities which have been used with some success are laser therapy, cryotherapy, hyperthermia and immunotherapy. The choice of treatment depends on the type of cancer and degree of dissemination. Unless the malignant growth is confined to a discrete area in the body, it is difficult to remove only malignant tissue without also affecting normal cells.

Malignant disorders commonly diagnosed in dogs and cats include but are not limited to lymphosarcoma, osteosarcoma, mammary tumors, mastocytoma, brain tumor, melanoma, adenosquamous carcinoma, carcinoid lung tumor, bronchial gland tumor, bronchiolar adenocarcinoma, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, retinoblastoma, Ewing's sarcoma, Wilms' tumor, Burkitt's lymphoma, microglioma, neuroblastoma, osteoclastoma, oral neoplasia, fibrosarcoma, osteosarcoma and

rhabdomyosarcoma. Other neoplasias in dogs include genital squamous cell carcinoma, transmissable venereal tumor, testicular tumor, seminoma, Sertoli cell tumor, hemangiopericytoma, histiocytoma, chloroma (granulocytic sarcoma), corneal papilloma, corneal squamous cell carcinoma, hemangiosarcoma, pleural mesothelioma, basal cell tumor, thymoma, stomach tumor, adrenal gland carcinoma, oral papillomatosis, hemangioendothelioma and cystadenoma. Additional malignancies diagnosed in cats include follicular lymphoma, intestinal lymphosarcoma, fibrosarcoma and pulmonary squamous cell carcinoma. The ferret, an ever-more popular house pet, is known to develop insulinoma, lymphoma, sarcoma, neuroma, pancreatic islet cell tumor, gastric MALT lymphoma and gastric adenocarcinoma.

Neoplasias affecting agricultural livestock include leukemia, hemangiopericytoma and bovine ocular neoplasia (in cattle); preputial fibrosarcoma, ulcerative squamous cell carcinoma, preputial carcinoma, connective tissue neoplasia and mastocytoma (in horses); hepatocellular carcinoma (in swine); lymphoma and pulmonary adenomatosis (in sheep); pulmonary sarcoma, lymphoma, Rous sarcoma, reticuloendotheliosis, fibrosarcoma, nephroblastoma, B-cell lymphoma and lymphoid leukosis (in avian species); retinoblastoma, hepatic neoplasia, lymphosarcoma (lymphoblastic lymphoma), plasmacytoid leukemia and swimbladder sarcoma (in fish), caseous lymphadenitis (CLA): chronic, infectious, contagious disease of sheep and goats caused by the bacterium *Corynebacterium pseudotuberculosis*, and contagious lung tumor of sheep caused by jaagsiekte.

In one aspect, a method for treating cancer is provided which involves administering the compositions of the invention to a subject having cancer. A "subject having cancer" is a subject that has been diagnosed with a cancer. In some embodiments, the subject has a cancer type characterized by a solid mass tumor. The solid tumor mass, if present, may be a primary tumor mass. A primary tumor mass refers to a growth of cancer cells in a tissue resulting from the transformation of a normal cell of that tissue. In most cases, the primary tumor mass is identified by the presence of a cyst, which can be found through visual inspection or palpation methods, or by irregularity in shape, texture or weight of the tissue.

However, some primary tumors are not palpable and can be detected only through medical imaging techniques such as X-rays (e.g., mammography), or by needle aspirations. The use of these latter techniques is more common in early detection. Molecular and

phenotypic analysis of cancer cells within a tissue will usually confirm if the cancer is endogenous to the tissue or if the lesion is due to metastasis from another site.

With respect to the prophylactic treatment methods, the invention is aimed at administering the compositions of the invention to a subject at risk of developing cancer. A subject at risk of developing a cancer is one who has a high probability of developing cancer. These subjects include, for instance, subjects having a genetic abnormality, the presence of which has been demonstrated to have a correlative relation to a higher likelihood of developing a cancer. Subjects exposed to cancer-causing agents such as tobacco, asbestos, or other chemical toxins are also subjects at risk of developing cancers used herein. When a subject at risk of developing a cancer is treated with an immunostimulatory nucleic acid, an antibody and optionally a cancer therapy, on a regular basis, such as monthly, the cancer growth will be prevented from initiating. This aspect of the invention is particularly advantageous when the subjects employed in certain trades which are exposed to cancer-causing agents on an ongoing basis. For example, many airborne, or inhaled, carcinogens such as tobacco smoke and asbestos have been associated with lung cancer.

A carcinogen is an agent capable of initiating development of malignant cancers. Exposure to carcinogens generally increases the risk of neoplasms in subjects, usually by affecting DNA directly. Carcinogens may take one of several forms such as chemical, electromagnetic radiation, or may be an inert solid body.

Substances for which there is sufficient evidence to establish a causal relationship in cancer in humans are referred to as confirmed human carcinogens. Included in this category are the following substances: Aflatoxins, Alcoholic beverages, Aluminium production, 4-aminobiphenyl, Arsenic and arsenic compounds, Asbestos, Manufacture of auramine, Azathioprine, Benzene, Benzidine, Beryllium and beryllium compounds, Betel quid with tobacco, Bis(chloromethyl)ether and chloromethyl methyl ether (technical grade), Boot and shoe manufacture and repair (occupational exposure), 1,4 Butanediol dimethanesulphonate (Myleran), Cadmium and cadmium compounds, Chlorambucil, Chlornaphazine, 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1 nitrosourea, Chloromethyl methyl ether (technical), Chromium compounds (hexavalent), Coal gasification, Coal tar pitches, Coal tars, Coke production, Cyclophosphamide, Cyclosporin, Erionite, Ethylene oxide, Furniture and cabinet making, Underground haematite mining with exposure to radon, Iron and steel founding, Isopropyl alcohol manufacture (strong acid process), Manufacture of magenta, Melphalan, 8-

Methoxypsoralen (Methoxsalen) plus ultraviolet radiation, Mineral oils-untreated and mildly-treated oils, MOPP and other combined chemotherapy for cancer, Mustard gas (sulphur mustard), 2-Naphthylamine, Nickel and nickel compounds (essentially sulphate and sulphide), Nonsteroidal estrogens (not necessarily all in group) includes diethylstilbestrol, Estrogen replacement therapy, and Combined oral contraceptives and sequential oral contraceptives, Steroidal estrogens (not all in group), Painter (occupational exposure as a painter), Phenacetin (analgesic mixtures containing), Rubber industry, Salted fish (Chinese style), Solar radiation, Shale oils, Soots, Sulphuric acid (occupational exposures to strong-inorganic-acid mists of sulphuric acid), Talc containing asbestiform fibres, Thiotepa, Tobacco products (smokeless), Tobacco smoke, Treosulphan, and Vinyl chloride.

Substances for which there is a lesser degree of evidence in humans but sufficient evidence in animal studies, or degrees of evidence considered unequivocal of mutagenicity in mammalian cells, are referred to as probable human carcinogens. This category of substances includes: Acrylamide, Acrylonitrile, Adriamycin, Anabolic steroids, Azacitidine, Benzanthracene, Benzidine-based dyes (technical grade), Direct Black 38, Direct Blue 6, Direct Brown 95, Benzopyrene1,3-Butadiene, Captafol, Bischloroethyl nitrosourea (BCNU), 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), Chloramphenicolpara-Chloro-ortho-toluidine and its strong acid salts, Chlorozotocin, Cisplatin, Creosotes, Dibenzanthracene, Diesel engine exhaust, Diethyl sulphate, Dimethylcarbamoyl chloride, Dimethyl sulphate, Epichlorohydrin, Ethylene dibromide, N-ethyl-N-nitrosourea, Formaldehyde, Glass manufacturing industry (occupational exposure), Art glass (glass containers and pressed ware), Hairdresser or barber (occupational exposure, probably dyes), Insecticide use (occupational), IQ (2-Amino-3-methylimidazo[4,5-f]quinoline), Mate drinking (hot), 5-Methoxypsoralen, 4,4'-Methylenebis(2-chloroaniline) (MOCA), N-Methyl-N-nitro-N-nitrosoguanidine (MNNG), N-Methyl-N-nitrosourea, Nitrogen mustard, N-Nitrosodiethylamine, N-Nitrosodimethylamine, Petroleum refining (occupational refining exposures), Phenacetin, Polychlorinated biphenyls, Procarbazine hydrochloride, Silica (crystalline), Styrene-7,8-oxide, Tris(1-azaridinyl)phosphine sulphide (Thiotepa), Tris(2,3-dibromopropyl) phosphate, Ultraviolet radiation: A, B and C including sunlamps and sunbeds, and Vinyl bromide.

Substances for which there is sufficient evidence in animal tests are referred to as possible human carcinogens. This category of substances includes: A-C(2-Amino-9H-

pyrido[2,3-b]indole), Acetaldehyde, Acetamide, AF-2[2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide, para-Aminoazobenzene, ortho-Aminoazobenzene, 2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole, Amitrole, ortho-Anisidine, Antimony trioxide, Aramite, Atrazine, Attapulgite, Azaserine, Benzo[b]fluoranthene, Benzo[j]fluoranthene, Benzo[k]fluoranthene, Benzyl violet, Bitumens (extracts of steam-refined and air-refined bitumens), Bleomycins, Bracken ferns, Bromodichloromethane, Butylated hydroxyanisole (BHA), á-Butyrolactone, Caffeic acid, Carbon black extract, Carbon tetrachloride, Carrageenan (degraded), Ceramic fibres, Chloramphenicol, Chlordane, Chlordecone, Chlorendic acid, Chlorinated paraffins of average carbon-chain length C12 and average degree of chlorination approx 60%, alpha-Chlorinated toluenes (not necessarily all in group), Benzotrichloride, para-Chloroaniline, Chloroform, Chlorophenols, Pentachlorophenol, 2,4,6-Trichlorophenol, Chlorophenoxy herbicides (not necessarily all in group), 4-Chloro-ortho-phenylenediamine, CI Acid Red 114, CI Basic Red 9, CI Direct Blue 15, Citrus Red No.2, Cobalt and cobalt compounds, Coffee (bladder), para-Cresidine, Cycasin, Dacarbazine, Dantron (1,8-dihydroxyanthraquinone), Daunomycin, DDT, N,N'-Diacetylbenzidine, 4,4'-Diaminodiphenyl ether, 2,4-Diaminotoluene, Dibenz[a,h]acridine, Dibenz[a,j]acridine, 7H-Dibenzo[c,g]carbazole, Dibenzo[a,e]pyrene, Dibenzo[a,h]pyrene, Dibenzo[a,i]pyrene, Dibenzo[a,l]pyrene, 1,2-Dibromo-3-chloropropane, para-Dichlorobenzene, 3,3'-Dichlorobenzene, 3,3'-Dichloro-4,4'-diaminodiphenyl ether, 1,2-Dichloroethane, Dichloromethane, 1,3-Dichloropropene (technical grade), Dichlorvos, Diepoxybutane, Diesel fuel (marine), Di(2-ethylhexyl)phthalate, 1,2-Diethylhydrazine, Diglycidyl resorcinol ether, Dihydrosafrole, Diisopropyl sulfate, 3,3'-Dimethoxybenzidine, para-Dimethylaminoazobenzene, trans-2-[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl[vinyl]-1,3,4-oxidiazole, 2,6-Dimethylaniline (2,6-Xylidene), 3,3'-Dimethylbenzidine (ortho-tolidine), Dimethylformamide, 1,1-Dimethylhydrazine, 1,2-Dimethylhydrazine, 1,6-Dinitropyrene, 1,8-Dinitropyrene, 1,4-Dioxane, Disperse Blue, 1Ethyl acrylate, Ethylene thiourea, Ethyl methanesulphonate, 2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole, Fuel oils (residual, heavy), Fusarium moniliforme (toxins derived from), Fumonisin B1; Fumonisin B2; Fusarin C, Gasoline, Gasoline engine exhausts, Glasswool, Glu-P-1 (2-Amino-6-methyldipyrido[1,2-a:3'2'-d]imidazole), Glu-P-2(-Aminodipyrido[1,2-a:3'2'-d]imidazole), Glycidaldehyde, Griseofulvin, HC Blue No 1, Heptachlor, Hexachlorobenzene, Hexachlorocyclohexanes Technical grades alpha isomer gamma isomer (lindane),

Hexamethylphosphoramide, Hydrazine, Indeno[1,2,3-cd]pyrene, Iron-dextran complex, Isoprene, Lasiocarpine, Lead and lead compounds (inorganic), Magenta (containing CI Basic Red 9), Man-made mineral fibres (see glasswool, rockwool, slagwool, and ceramic fibres), MeA-a-C (2-Amino-3-methyl-9H-pyrido[2,3-b]indole), MeIQ (2-Amino-3,4-dimethylimidazo[4,5-f]-quinolone), MeIQx (2-Amino-3,8-dimethylamidazo[4,5-f]quinoxaline), Methylmercury compounds (methylmercuric chloride), Melphalan, 2-Methylaziridine, Methylazoxymethanol and its acetate, 5-Methylchrysene, 4,4'-Methylenebis(2-methylaniline), 4,4'-Methylenedianiline, Methylmethanesulphonate, 2-methyl-1-nitroanthraquinone (uncertain purity), N-methyl-N-nitrosourethane, Methylthiouracil, Metronidazole, Mirex, Mitomycin, Monocrotaline 5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone, Nafenopin, Niridazole, 5-Nitroacenaphthene, 6-Nitrochrysene, Nitrofen (technical grade), 2-Nitrofluorene1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone, N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide, Nitrogen mustard, N-oxide, Nitrolotriacetic acid and its salts, 2-Nitropropane1-Nitropyrene, 4-Nitropyrene, N-Nitrosodi-n-butylamine, N-Nitrosodiethanolamine, N-Nitrosodi-n-propylamine, 3-(N-Nitrosomethylamino)propionitrile, 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N-Nitrosomethylethylamine, N-Nitrosomethylvinylamine, N-Nitrosomorpholine, N-Nitrosonornicotine, N-Nitrosopiperidene, N-Nitrosopyrrolidine, N-Nitrososarcosine, Ochratoxin A, Oil Orange, Panfuran S (containing dihydroxymethylfuratzine), Phenazopyridine hydrochloride, Phenobarbital, Phenoxybenzamine hydrochloride, Phenyl glycidyl ether, PhenytoinPhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, Pickled vegetables, traditional Asian, Polybrominated biphenyls, Ponceau MXPonceau 3R, Potassium bromate, 1,3-Propane sultone, Propylene oxide, Progestins, Medroxyprogesterone acetate, á-Propiolactone, Propylthiouracil, Rockwool, Saccharin, Safrole, Slagwool, Sodium ortho-phenylphenate, Sterigmatocystin, Streptozotocin, Styrene, Sulfallate, 2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD), Tetrachloroethylene, Textile manufacturing (occupational exposures), Thiocetamide, 4,4'-Thiodianiline, Thiourea, Toluene, diisocyanatesortho-Toluidine, Toxaphene (polychlorinated camphenes), Trichlormethine (trimustine hydrochloride), Trp-P-1 (3-Amino-1,4-dimethyl-5-H-pyrido[4,3-b]indole), Trp-P-2 (3-Amino-1-methyl-5H-pyrido[4,3-b]indole), Trypan blue, Uracil mustard, Urethane, 4-Vinylcyclohexene, 4-Vinylcyclohexene diepoxide, Welding fumes, Wood industries and Carpentry and joinery.

Subjects at risk of developing cancer also include those who have a genetic predisposition to cancer. In many cases, genetic predisposition to cancer can be identified by studying the occurrence of cancer in family members. Examples of genetic predisposition to common forms of cancer include, but are not limited to, mutation of BRCA1 and BRCA2 in familial breast cancer, mutation of APC in familial colony cancer (familial polyposis coli), mutation of MSH2 and MLH1 in hereditary nonpolyposis colon cancer (HNPCC), mutation of p53 in Li-Fraumeni syndrome, mutation of Rb1 in retinoblastoma, mutation of RET in multiple endocrine neoplasia type 2 (MEN2), mutation of VHL in renal cancer and mutation of WT1 in Wilms' tumor. Other cancers for which a familial predisposition has been identified include ovarian, prostate, melanoma and lung cancer.

It has been estimated that almost half of all currently diagnosed cancers will be treated with some form of cancer medicament. However, many forms of cancer, including melanoma, colorectal, prostate, endometrial, cervical and bladder cancer, do not respond well to treatment with cancer medicaments. In fact, only about 5-10 percent of cancers can be cured using cancer medicaments alone. These include some forms of leukemias and lymphomas, testicular cancer, choriocarcinoma, Wilms' tumor, Ewing's sarcoma, neuroblastoma, small-cell lung cancer and ovarian cancer. Treatment of still other cancers, including breast cancer, requires a combination therapy of surgery or radiotherapy in conjunction with a cancer medicament.

The immunostimulatory nucleic acids are administered in combination with antibodies which specifically bind to cancer cell surface antigens. These antibodies include but are not limited to anti-CD20 antibodies, anti-CD40 antibodies, anti-CD19 antibodies, anti-CD22 antibodies, anti-HLA-DR antibodies, anti-CD80 antibodies, anti-CD86 antibodies, anti-CD54 antibodies, and anti-CD69 antibodies. These antibodies are available from commercial sources or may be synthesized de novo.

Commercially available anti-CD20 antibodies include but are not limited to those presented in Table 1 below.

Table 1. Commercially Available Anti-CD20 Antibodies.

Product/Supplier	Catalog #
Monoclonal Antibody to CD20, Human, Purified, 100 µg Alexis Corp.	ANC-169-020

Product/Supplier	Catalog #
CD20, B-Cell Bab Mouse: anti-Human Clone: L26 Isotype: IgG2a, Kappa; Concentrated Biomeda Corporation	V6021
CD20, B-Cell Mab Mouse: anti-Human Clone: L26 Isotype: IgG2a, Kappa; Concentrated Biomeda Corporation	V1018
CD20, B-Cell MAb Mouse: anti-Human Clone: L26 Isotype: IgG2a, Kappa; Dehydrated Biomeda Corporation	K026
CD20, B-Cell Mab Mouse: anti-Human Clone: L26 Isotype: IgG2a, Kappa; Prediluted Biomeda Corporation	058D
Mouse anti-Human CD20 BioSource International	AHS2022
Mouse anti-Human CD20 BioSource International	AHS2001
Mouse anti-Human CD20 BioSource International	AHS2028
Mouse anti-Human CD20 BioSource International	AHS2002
Mouse anti-Human CD20 BioSource International	AHS2021
Mouse Anti-CD20, B-Cell, Human IgG2a Antibody, Kappa, Supernatant, Clone L26,1 mL BIOTREND Chemikalien GmbH	MOB004
AnTesti-CD20, Human, Mouse, 100 μg Calbiochem	217670
Mouse Monoclonal Anti-(Human CD20) IgG3 Antibody, Clone HI47, 0.5 mL Caltag Laboratories	MHCD2000
Mouse Monoclonal Anti-(Human CD20) IgG3 Antibody, Clone B-ly 1, 1 mL Caltag Laboratories	MHCD2000-4
Mouse Monoclonal Anti-(Human CD20), Mature B-cell) IgG1 Antibody, Clone MEM-97, 1 mL Caltag Laboratories	MON1111
CD20, B-cell, Mouse Anti-Human, Clone: L26, Isotype: IgG2a, kappa, Ready-to-Use, LSAB2, EnVision & EnVision Doublestain, Monoclonal Antibody, 12 mL DAKO Corp.	N150230
CD20, B-cell, Mouse Anti-Human, Clone: L26, Isotype: IgG2a, kappa, Ready-to-Use, LSAB2, EnVision & EnVision Doublestain, Monoclonal Antibody, Packaged for DAKO Autostainer, 33 mL\ DAKO Corp.	N150289
CD20, L26 B-cell Marker, Mouse Anti-Human, Human, Monoclonal Antibody, 1 mL DAKO Corp.	M075501
CD20, L26 B-cell Marker, Mouse Anti-Human Monoclonal Antibody, 1 mL DAKO Corp.	M077401
MxH B cell, CD20 RTU, 12 mL DAKO Corp.	L185030

Product/Supplier	Catalog #
Monoclonal Anti-B-Cell, CD20 IgG2a Antibody, Clone L26, concentrated, 1 mL Diagnostic BioSystems	Mob 004
Monoclonal Anti-CD20, B-Cell IgG1 Antibody, Clone 7D1, concentrated, 1 mL Diagnostic BioSystems	Mob 241
Monoclonal Anti-CD20, B-Cell IgG2a Antibody, Clone L26, Concentrated, 1 mL Diagnostic BioSystems	Mob 004-01
Rabbit Polyclonal Anti-CD20, B-cell Antibody, Concentrated, 1 mL Diagnostic Biosystems	RP 041
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1455
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	C06603858
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1342
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1565
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1454
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6604106
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6603446
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1456
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1451
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6602381
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM1925
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6602140
CD20, Pan B-cell marker, Mouse Anti-Human, Monoclonal Antibody, 1 mL DAKO Corp.	M077401
MxH B Cell, CD20 RTU, 12 mL DAKO Corp.	L185030
Monoclonal Anti-B-Cell, CD20 IgG2a Antibody, Clone L26, Concentrated, 1 mL Diagnostic BioSystems	Mob 004
Monoclonal Anti-CD20, B-Cell IgG1 Antibody, Clone 7D1, Concentrated,. 1 mL Diagnostic BioSystems	Mob 241
Monoclonal Anti-CD20, B-Cell IgG2a Antibody, Clone L26, Concentrated, 1 mL Diagnostic BioSystems	Mob 004-01
Rabbit Polyclonal Anti-CD20, B-cell Antibody, Concentrated, 1 mL Diagnostic BioSystems	RP 041
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1455

Product/Supplier	Catalog #
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6603858
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1342
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1565
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1454
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6604106
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6603446
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1456
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1451
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6602381
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	COIM 1925
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6602140
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6602471
CD20 (B Cell) InnoGenex	AM-1165-11
Coulter* Antibodies to Human CDs::CD20 Fisher Scientific Co.	CO6602471
CD20 (B Cell) InnoGenex	AM-1165-11
CD20 (B Cell), Unpurified (0.1 mg/0.1 mL), Clone: B1, Isotype: InnoGenex	AM-1165-11
Mouse Monoclonal Anti-CD20 Ab-1 (B- Cell Marker) IgG_{2a}/κ Antibody, Clone: L26, Workshop, 0.1 mL Lab Vision Corp.	MS-340-SO
Mouse Monoclonal Anti-CD20 Ab-1 (B- Cell Marker) IgG_{2a}/κ Antibody, Clone: L26, Workshop, 0.5 mL Lab Vision Corp.	MS-340-S1
Mouse Monoclonal Anti-CD20 Ab-1 (B- Cell Marker) IgG_{2a}/κ Antibody, Clone: L26, Workshop, 1.0 mL Lab Vision Corp.	MS-340-S
Mouse Monoclonal Anti-CD20 Ab-1 (B- Cell Marker) IgG_{2a}/κ Antibody, Clone: L26, Workshop, 7.0 mL Lab Vision Corp.	MS-340-R7
Mouse Monoclonal Anti-CD20 Ab-1 (B- Cell Marker) IgG_{2a}/κ Antibody, Clone: B9E9, Workshop V; 100 μg Lab Vision Corp.	MS-431-P1

Product/Supplier	Catalog #
Mouse Monoclonal Anti-CD20 Ab-1 (B- Cell Marker) IgG$_{2a}$/κ Antibody, Clone: B9E9, Workshop V; 200 μg Lab Vision Corp.	MS-431-P
Mouse Monoclonal Anti-CD20 (Ab-1 (B- Cell Marker) IgG$_{2a}$/κ Antibody, Clone: B9E9, Workshop V; 20 μg Lab Vision Corp.	MS-431-PO
Mouse Monoclonal Anti-CD20 Ab-1 (B- Cell Marker) IgG$_1$/κ Antibody, Clone: 93-1B3, Workshop V; Code: CD20.4, 100 μg Lab Vision Corp.	MS-758-P1
Mouse Monoclonal Anti-CD20 Ab-3 (B- Cell Marker) IgG$_1$/κ Antibody, Clone: 93-1B3, Workshop V; Code: CD20.4, 200 μg Lab Vision Corp.	MS-758-P
Mouse Monoclonal Anti-CD20 Ab-3 (B- Cell Marker) IgG$_1$/ Antibody, Clone: 93-1B3, Workshop V; Code: CD20.4 Lab Vision Corp.	MS-758-PO
Human CD20, B Cell, 6 mL Maxim Biotech Inc.	MAB-0020
Mouse Monoclonal Anti-B Cell, CD20 IgG$_{2a}$, κ Antibody, Concentrate, 1 mL Scytek	A9004C
Mouse Monoclonal Anti-B Cell, CD20 IgG$_{2a}$, κ Antibody, Ready-to-Use, 1 mL Scytek	A20003
Mouse Monoclonal Anti-CD20, B Cell IgG$_{2a}$, κ Antibody, Concentrate, 1 mL Scytek	A9001C (Clone: L26)
Mouse Monoclonal Anti-CD20, B Cell IgG$_{2a}$, κ Antibody, Ready-to-Use, 6 mL Scytek	A00003
Mouse Monoclonal Anti-(Human CD20 IgG1 Antibody, Clone 7D1, 1 mL Serotec, Inc.	MCA 1807
Mouse Monoclonal Anti-(Human CD20 IgG1 Antibody, Clone AT80, 0.2 mg Serotec, Inc.	MCA 1822
Mouse Monoclonal Anti-(Human CD20 IgG2b Antibody, Clone 2H7, 0.2 mg Serotec, Inc.	MCA 1710
Antibody Panels, Hematopoietic Markers, Lymphocyte Related Antigens, CD20, B Cell, Clone L26, Concentrated, 1 mL, Ab Source Mouse, Ab# 324 Signet Pathology Systems, Inc.	324-01
Antibody Panels, Hematopoietic Markers, Lymphocyte Related Antigens, CD20, B Cell, Clone L26, Level 1, 3 mL, Ab 324 Signet Pathology Systems, Inc.	324-13

Product/Supplier	Catalog #
Antibody Panels, Hematopoietic Markers, Lymphocyte Related Antigens, CD20, B Cell, Clone L26, level 1, 6 mL, Ab Source Mouse, Ab# 324 Signet Pathology Systems, Inc.	324-16
Antibody Panels, Hematopoietic Markers, Lymphocyte Related Antigens, CD20, B Cell, Clone L26, Level 2, 6 mL, Ab Source Mouse, Ab# 324 Signet Pathology Systems, Inc.	324-26
Monoclonal Mouse anti-CD20, B9E9, Epitope-Affinity Purified-Unconjugated, IgG_{2a}-κ, 200 μg Zymed Laboratories, Inc.	07-2003

Antibodies are well known to those of ordinary skill in the science of immunology. As used herein, the term "antibody" means not only intact antibody molecules but also fragments of antibody molecules retaining specific binding ability. Such fragments are also well known in the art and are regularly employed both in vitro and in vivo. In particular, as used herein, the term "antibody" means not only intact immunoglobulin molecules but also the well-known active fragments $F(ab')_2$, and Fab. $F(ab')_2$, and Fab fragments which lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding of an intact antibody. Wahl RL et al., *J Nucl Med* 24:316-25 (1983). Antibody fragments which are particularly useful according to the methods of the invention are those which are bispecific and constructed to enhance FcR binding, e.g., include an Fc portion. These include, but are not limited to Medarex antibodies (MDX-210, 220, 22, 447, and 260). Other non-Fc containing fragments which interact with the antigens induced on the cell surface are also useful. These are particularly useful in combination with immunotoxins and/or radioactivity. The fragments can be delivered separately from the immunotoxins or radioactivity or conjugated thereto (e.g., radiolabled antibodies or antibody fragments).

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity-determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity-determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as "chimeric" antibodies. A "humanized monoclonal antibody" as used herein is a human monoclonal antibody or functionally active fragment thereof having human constant regions and a binding CDR3 region from a mammal of a species other than a human. Humanized monoclonal antibodies may be made by any method known in the art. Humanized monoclonal antibodies, for example, may be constructed by replacing the non-CDR regions of a non-human mammalian antibody with similar regions of human antibodies while retaining the epitopic specificity of the original antibody. For example, non-human CDRs and optionally some of the framework regions may be covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. There are entities in the United States which will synthesize humanized antibodies from specific murine antibody regions commercially, such as Protein Design Labs (Mountain View California).

European Patent Application 0239400, the entire contents of which is hereby incorporated by reference, provides an exemplary teaching of the production and use of humanized monoclonal antibodies in which at least the CDR portion of a murine (or other non-human mammal) antibody is included in the humanized antibody. Briefly, the following methods are useful for constructing a humanized CDR monoclonal antibody including at least a portion of a mouse CDR. A first replicable expression vector including a suitable promoter operably linked to a DNA sequence encoding at least a variable domain of an Ig heavy or light chain and the variable domain comprising framework regions from a human antibody and a CDR region of a murine antibody is prepared. Optionally a second replicable expression vector is prepared which includes a suitable promoter operably linked to a DNA sequence encoding at least the variable domain of a complementary human Ig light or heavy chain respectively. A cell line is then transformed with the vectors. Preferably the cell line is

an immortalized mammalian cell line of lymphoid origin, such as a myeloma, hybridoma, trioma, or quadroma cell line, or is a normal lymphoid cell which has been immortalized by transformation with a virus. The transformed cell line is then cultured under conditions known to those of skill in the art to produce the humanized antibody.

As set forth in European Patent Application 0239400 several techniques are well known in the art for creating the particular antibody domains to be inserted into the replicable vector. (Preferred vectors and recombinant techniques are discussed in greater detail below.) For example, the DNA sequence encoding the domain may be prepared by oligonucleotide synthesis. Alternatively a synthetic gene lacking the CDR regions in which four framework regions are fused together with suitable restriction sites at the junctions, such that double-stranded synthetic or restricted subcloned CDR cassettes with sticky ends could be ligated at the junctions of the framework regions. Another method involves the preparation of the DNA sequence encoding the variable CDR containing domain by oligonucleotide site-directed mutagenesis. Each of these methods is well known in the art. Therefore, those skilled in the art may construct humanized antibodies containing a murine CDR region without destroying the specificity of the antibody for its epitope.

Human monoclonal antibodies may be made by any of the methods known in the art, such as those disclosed in U.S. Patent No. 5,567,610, issued to Borrebaeck et al., U.S. Patent No. 5,565,354, issued to Ostberg, U.S. Patent No. 5,571,893, issued to Baker et al, Kozbor D et al., *J Immunol* 133:3001-5 (1984), Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc, New York, 1987), and Boerner P et al., *J Immunol* 147:86-95 (1991). In addition to the conventional methods for preparing human monoclonal antibodies, such antibodies may also be prepared by immunizing transgenic animals that are capable of producing human antibodies (e.g., Jakobovits A et al., *Proc Natl Acad Sci USA* 90:2551-5 (1993); Jakobovits A et al., *Nature* 362:255-8 (1993); Bruggermann et al., Year in Immunology 7:33 (1993); and U.S. Patent No. 5,569,825 issued to Lonberg).

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the

complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an $F(ab')_2$ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Other antibodies useful according to the invention are antibodies of the IgG1 isotype. As mentioned above, anti-IgG1 isotype antibody as used herein refers to a human or humanized anti-IgG1 unless otherwise specified. IgG1 isotype antibodies are well known in the art and include at least the antibodies listed in Table 2 below.

Table 2: Cancer Immunotherapies In Development Or On The Market.

Marketer	Brand Name (Generic Name)	Indication
IDEC/Genentech, Inc./Hoffmann-LaRoche (first monoclonal antibody licensed for the treatment of cancer in the U.S.)	Rituxan™ (rituximab, Mabthera) (IDEC-C2B8, chimeric murine/human anti-CD20 MAb)	non-Hodgkin's lymphoma
Genentech/Hoffmann-La Roche	Herceptin, anti-Her2 hMAb	Breast/ovarian
Cytogen Corp.	Quadramet (CYT-424) radiotherapeutic agent	Bone metastases
Centocor/Glaxo/Ajinomoto	Panorex® (17-1A) (murine monoclonal antibody)	Adjuvant therapy for colorectal (Dukes-C)
Centocor/Ajinomoto	Panorex® (17-1A) (chimeric murine monoclonal antibody)	Pancreatic, lung, breast, ovary
IDEC	IDEC-Y2B8 (murine, anti-CD20 MAb labeled with Yttrium-90)	non-Hodgkin's lymphoma
ImClone Systems	BEC2 (anti-idiotypic MAb, mimics the GD_3 epitope) (with BCG)	Small cell lung
ImClone Systems	C225 (chimeric monoclonal antibody to epidermal growth factor receptor (EGFr))	Renal cell
Techniclone International/Alpha Therapeutics	Oncolym (Lym-1 monoclonal antibody linked to 131 iodine)	non-Hodgkin's lymphoma
Protein Design Labs	SMART M195 Ab, humanized	Acute myleoid leukemia

Marketer	Brand Name (Generic Name)	Indication
Techniclone Corporation/Cambridge Antibody Technology	^{131}I LYM-1 (Oncolym™)	non-Hodgkin's lymphoma
Aronex Pharmaceuticals, Inc.	ATRAGEN®	Acute promyelocytic leukemia
ImClone Systems	C225 (chimeric anti-EGFr monoclonal antibody) + cisplatin or radiation	Head & neck, non-small cell lung cancer
Altarex, Canada	Ovarex (B43.13, anti-idiotypic CA125, mouse MAb)	Ovarian
Coulter Pharma (Clinical results have been positive, but the drug has been associated with significant bone marrow toxicity)	Bexxar (anti-CD20 Mab labeled with ^{131}I)	non-Hodgkin's lymphoma
Aronex Pharmaceuticals, Inc.	ATRAGEN®	Kaposi's sarcoma
IDEC Pharmaceuticals Corp./Genentech	Rituxan™ (MAb against CD20) pan-B Ab in combo. with chemotherapy	B cell lymphoma
LeukoSite/Ilex Oncology	LDP-03, huMAb to the leukocyte antigen CAMPATH	Chronic lymphocytic leukemia (CLL)
Center of Molecular Immunology	ior t6 (anti CD6, murine MAb) CTCL	Cancer
Medarex/Novartis	MDX-210 (humanized anti-HER-2 bispecific antibody)	Breast, ovarian
Medarex/Novartis	MDX-210 (humanized anti-HER-2 bispecific antibody)	Prostate, non-small cell lung, pancreatic, breast
Medarex	MDX-11 (complement activating receptor (CAR) monoclonal antibody)	Acute myelogenous leukemia (AML)
Medarex/Novartis	MDX-210 (humanized anti-HER-2 bispecific antibody)	Renal and colon
Medarex	MDX-11 (complement activating receptor (CAR) monoclonal antibody)	Ex vivo bone marrow purging in acute myelogenous leukemia (AML)
Medarex	MDX-22 (humanized bispecific antibody, MAb-conjugates) (complement cascade activators)	Acute myleoid leukemia
Cytogen	OV103 (Yttrium-90 labelled antibody)	Ovarian
Cytogen	OV103 (Yttrium-90 labelled antibody)	Prostate
Aronex Pharmaceuticals, Inc.	ATRAGEN®	non-Hodgkin's lymphoma
Glaxo Wellcome plc	3622W94 MAb that binds to EGP40 (17-1A) pancarcinoma antigen on adenocarcinomas	non-small cell lung, prostate (adjuvant)
Genentech	Anti-VEGF, RhuMAb (inhibits angiogenesis)	Lung, breast, prostate, colorectal
Protein Design Labs	Zenapax (SMART Anti-Tac (IL-2 receptor) Ab, humanized)	Leukemia, lymphoma
Protein Design Labs	SMART M195 Ab, humanized	Acute promyelocytic leukemia

Marketer	Brand Name (Generic Name)	Indication
ImClone Systems	C225 (chimeric anti-EGFr monoclonal antibody) + taxol	Breast
ImClone Systems (licensed from RPR)	C225 (chimeric anti-EGFr monoclonal antibody) + doxorubicin	prostate
ImClone Systems	C225 (chimeric anti-EGFr monoclonal antibody) + adriamycin	prostate
ImClone Systems	BEC2 (anti-idiotypic MAb, mimics the GD_3 epitope)	Melanoma
Medarex	MDX-210 (humanized anti-HER-2 bispecific antibody)	Cancer
Medarex	MDX-220 (bispecific for tumors that express TAG-72)	Lung, colon, prostate, ovarian, endometrial, pancreatic and gastric
Medarex/Novartis	MDX-210 (humanized anti-HER-2 bispecific antibody)	Prostate
Medarex/Merck KgaA	MDX-447 (humanized anti-EGF receptor bispecific antibody)	EGF receptor cancers (head & neck, prostate, lung, bladder, cervical, ovarian)
Medarex/Novartis	MDX-210 (humanized anti-HER-2 bispecific antibody)	Comb. Therapy with G-CSF for various cancers, esp. breast
IDEC	MELIMMUNE-2 (murine monoclonal antibody therapeutic vaccine)	Melanoma
IDEC	MELIMMUNE-1 (murine monoclonal antibody therapeutic vaccine)	Melanoma
Immunomedics, Inc.	CEACIDE™ (I-131)	Colorectal and other
NeoRx	Pretarget™ radioactive antibodies	non-Hodgkin's B cell lymphoma
Novopharm Biotech, Inc.	NovoMAb-G2 (pancarcinoma specific Ab)	Cancer
Techniclone Corporation/ Cambridge Antibody Technology	TNT (chimeric MAb to histone antigens)	Brain
Techniclone International/Cambridge Antibody Technology	TNT (chimeric MAb to histone antigens)	Brain
Novopharm	Gliomab-H (Monoclonals - Humanized Abs)	Brain, melanomas, neuroblastomas
Genetics Institute/AHP	GNI-250 Mab	Colorectal
Merck KgaA	EMD-72000 (chimeric-EGF antagonist)	Cancer
Immunomedics	LymphoCide (humanized LL2 antibody)	non-Hodgkin's B-cell lymphoma
Immunex/AHP	CMA 676 (monoclonal antibody conjugate)	Acute myelogenous leukemia
Novopharm Biotech, Inc.	Monopharm-C	Colon, lung, pancreatic
Novopharm Biotech, Inc.	4B5 anti-idiotype Ab	Melanoma, small-cell lung

Marketer	Brand Name (Generic Name)	Indication
Center of Molecular Immunology	ior egf/r3 (anti EGF-R humanized Ab)	Radioimmunotherapy
Center of Molecular Immunology	ior c5 (murine MAb colorectal) for radioimmunotherapy	Colorectal
Creative BioMolecules/ Chiron	BABS (biosynthetic antibody binding site) Proteins	Breast cancer
ImClone Systems/Chugai	FLK-2 (monoclonal antibody to fetal liver kinase-2 (FLK-2))	Tumor-associated angiogenesis
ImmunoGen, Inc.	Humanized MAb/small-drug conjugate	Small-cell lung
Medarex, Inc.	MDX-260 bispecific, targets GD-2	Melanoma, glioma, neuroblastoma
Procyon Biopharma, Inc.	ANA Ab	Cancer
Protein Design Labs	SMART 1D10 Ab	B-cell lymphoma
Protein Design Labs/Novartis	SMART ABL 364 Ab	Breast, lung, colon
Immunomedics, Inc.	ImmuRAIT-CEA	Colorectal

In some embodiments the nucleic acid and antibody are administered in combination with a cancer therapy. As used herein, a "cancer therapy" refers to an agent which prevents growth of a cancer cell by decreasing or slowing the rate of growth, by inhibiting growth altogether, or by killing or inducing apoptosis of the cancer cell. Thus, as used herein, "treating cancer" includes preventing the development of a cancer, reducing the symptoms of cancer, and/or inhibiting the growth of an established cancer. In other aspects, the cancer therapy is administered to a subject at risk of developing a cancer for the purpose of reducing the risk of developing the cancer. Various types of medicaments for the treatment of cancer are described herein. For the purpose of this specification, cancer therapies are classified as chemotherapeutic agents, cancer vaccines, hormone therapy, biological response modifiers, surgical procedures, and radiotherapy aimed at treating cancer. Additionally, the methods of the invention are intended to embrace the use of more than one cancer therapy along with the immunostimulatory nucleic acids and antibody. As an example, where appropriate, the immunostimulatory nucleic acids may be administered with a both a chemotherapeutic agent and a radiotherapy.

Cancer therapies function in a variety of ways. Some cancer therapies work by targeting physiological mechanisms that are specific to tumor cells. Examples include the targeting of specific genes and their gene products (i.e., proteins primarily) which are mutated in cancers. Such genes include but are not limited to oncogenes (e.g., Ras, Her2, bcl-2), tumor suppressor genes (e.g., EGF, p53, Rb), and cell cycle targets (e.g., CDK4, p21,

telomerase). Cancer therapies can alternately target signal transduction pathways and molecular mechanisms which are altered in cancer cells.

Other cancer therapies target cells other than cancer cells. For example, some medicaments prime the immune system to attack tumor cells (i.e., cancer vaccines). Still other medicaments, called angiogenesis inhibitors, function by attacking the blood supply of solid tumors. Since the most malignant cancers are able to metastasize (i.e., exit the primary tumor site and seed a distal tissue, thereby forming a secondary tumor), medicaments that impede this metastasis are also useful in the treatment of cancer. Angiogenic mediators include basic FGF, VEGF, angiopoietins, angiostatin, endostatin, TNF-α, TNP-470, thrombospondin-1, platelet factor 4, CAI, and certain members of the integrin family of proteins. One category of this type of medicament is a metalloproteinase inhibitor, which inhibits the enzymes used by the cancer cells to exit the primary tumor site and extravasate into another tissue.

As used herein, chemotherapeutic agents encompass both chemical and biological agents. These agents function to inhibit a cellular activity which the cancer cell is dependent upon for continued survival. Categories of chemotherapeutic agents include alkylating/alkaloid agents, antimetabolites, hormones or hormone analogs, and miscellaneous antineoplastic drugs. Most if not all of these agents are directly toxic to cancer cells and do not require immune stimulation. Chemotherapeutic agents which are currently in development or in use in a clinical setting are shown in Table 3 below.

Table 3: Cancer Drugs In Development Or On The Market.

Marketer	Brand Name	Generic Name	Indication
Abbott	TNP 470/AGM 1470	Fragyline	Anti-Angiogenesis in Cancer
Takeda	TNP 470/AGM 1470	Fragyline	Anti-Angiogenesis in Cancer
Scotia	Meglamine GLA	Meglamine GLA	Bladder Cancer
Medeva	Valstar	Valrubicin	Bladder Cancer - Refractory in situ carcinoma
Medeva	Valstar	Valrubicin	Bladder Cancer - Papillary Cancer
Rhone Poulenc	Gliadel Wafer	Carmustaine + Polifepr Osan	Brain Tumor
Warner Lambert	Undisclosed Cancer (b)	Undisclosed Cancer (b)	Cancer
Bristol-Myers Squibb	RAS Famesyl Transferase Inhibitor	RAS FamesylTransferase Inhibitor	Cancer
Novartis	MMI 270	MMI 270	Cancer
Bayer	BAY 12-9566	BAY 12-9566	Cancer
Merck	Famesyl Transferase Inhibitor	Famesyl Transferase Inhibitor	Cancer (Solid tumors - pancreas, colon, lung, breast)
Pfizer	PFE	MMP	Cancer, angiogenesis

Marketer	Brand Name	Generic Name	Indication
Pfizer	PFE	Tyrosine Kinase	Cancer, angiogenesis
Lilly	MTA/LY 231514	MTA/LY 231514	Cancer Solid Tumors
Lilly	LY 264618/Lometexol	Lometexol	Cancer Solid Tumors
Scotia	Glamolec	LiGLA (lithium-gamma linolenate)	Cancer, pancreatic, breast, colon
Warner Lambert	CI-994	CI-994	Cancer, Solid Tumors / Leukemia
Schering AG	Angiogenesis inhibitor	Angiogenesis Inhibitor	Cancer / Cardio
Takeda	TNP-470	n/k	Malignant Tumor
Smithkline Beecham	Hycamtin	Topotecan	Metastatic Ovarian Cancer
Novartis	PKC 412	PKC 412	Multi-Drug Resistant Cancer
Novartis	Valspodar	PSC 833	Myeloid Leukemia/Ovarian Cancer
Immunex	Novantrone	Mitoxantrone	Pain related to hormone refractory prostate cancer.
Warner Lambert	Metaret	Suramin	Prostate
Genentech	Anti-VEGF	Anti-VEGF	Prostate / Breast / Colorectal / NSCL Cancer
British Biotech	Batimastat	Batimastat (BB94)	Pterygium
Eisai	E 7070	E 7070	Solid Tumors
Biochem Pharma	BCH-4556	BCH-4556	Solid Tumors
Sankyo	CS-682	CS-682	Solid Tumors
Agouron	AG2037	AG2037	Solid Tumors
IDEC Pharma	9-AC	9-AC	Solid Tumors
Agouron	VEGF/b-FGF Inhibitors	VEGF/b-FGF Inhibitors	Solid Tumors
Agouron	AG3340	AG3340	Solid Tumors / Macular Degeneration
Vertex	Incel	VX-710	Solid Tumors - IV
Vertex	VX-853	VX-853	Solid Tumors - Oral
Zeneca	ZD 0101 (inj)	ZD 0101	Solid Tumors
Novartis	ISI 641	ISI 641	Solid Tumors
Novartis	ODN 698	ODN 698	Solid Tumors
Tanube Seiyaku	TA 2516	Marimistat	Solid Tumors
British Biotech	Marimastat	Marimastat (BB 2516)	Solid Tumors
Celltech	CDP 845	Aggrecanase Inhibitor	Solid Tumors / Breast Cancer
Chiroscience	D2163	D2163	Solid Tumors / Metastases
Warner Lambert	PD 183805	PD 183805	
Daiichi	DX8951f	DX8951f	Anti-Cancer
Daiichi	Lemonal DP 2202	Lemonal DP 2202	Anti-Cancer
Fujisawa	FK 317	FK 317	Anticancer Antibiotic
Chugai	Picibanil	OK-432	Antimalignant Tumor
Nycomed Amersham	AD 32/valrubicin	Valrubicin	Bladder Cancer-Refractory In situ Carcinoma
Nycomed Amersham	Metastron	Strontium Derivative	Bone Cancer (adjunct therapy, Pain)
Schering Plough	Temodal	Temozolomide	Brain Tumors
Schering Plough	Temodal	Temozolonide	Brain Tumors
Liposome	Evacet	Doxorubicin, Liposomal	Breast Cancer
Nycomed Amersham	Yewtaxan	Paclitaxel	Breast Cancer Advanced, Ovarian Cancer Advanced

Marketer	Brand Name	Generic Name	Indication
Bristol-Myers Squibb	Taxol	Paclitaxel	Breast Cancer Advanced, Ovarian Cancer Advanced, NSCLC
Roche	Xeloda	Capecitabine	Breast Cancer, Colorectal Cancer
Roche	Furtulon	Doxifluridine	Breast Cancer, Colorectal Cancer, Gastric Cancer
Pharmacia & Upjohn	Adriamycin	Doxorubicin	Breast Cancer, Leukemia
Ivax	Cyclopax	Paclitaxel, Oral	Breast/Ovarian Cancer
Rhone Poulenc	Oral Taxoid	Oral Taxoid	Broad Cancer
AHP	Novantrone	Mitoxantrone	Cancer
Sequus	SPI-077	Cisplatin, Stealth	Cancer
Hoechst	HMR 1275	Flavopiridol	Cancer
Pfizer	CP-358, 774	EGFR	Cancer
Pfizer	CP-609, 754	RAS Oncogene Inhibitor	Cancer
Bristol-Myers Squibb	BMS-182751	Oral Platinum	Cancer (Lung, Ovarian)
Bristol-Myers Squibb	UFT (Tegafur/Uracil)	UFT (Tegafur/Uracil)	Cancer Oral
Johnson & Johnson	Ergamisol	Levamisole	Cancer Therapy
Glaxo Wellcome	Eniluracil/776C85	5FU Enhancer	Cancer, Refractory Solid & Colorectal Cancer
Johnson & Johnson	Ergamisol	Levamisole	Colon Cancer
Rhone Poulenc	Campto	Irinotecan	Colorectal Cancer, Cervical Cancer
Pharmacia & Upjohn	Camptosar	Irinotecan	Colorectal Cancer, Cervical Cancer
Zeneca	Tomudex	Ralitrexed	Colorectal Cancer, Lung Cancer, Breast Cancer
Johnson & Johnson	Leustain	Cladribine	Hairy Cell Leukaemia
Ivax	Paxene	Paclitaxel	Kaposi Sarcoma
Sequus	Doxil	Doxorubicin, Liposomal	KS/Cancer
Sequus	Caelyx	Doxorubicin, Liposomal	KS/Cancer
Schering AG	Fludara	Fludarabine	Leukaemia
Pharmacia & Upjohn	Pharmorubicin	Epirubicin	Lung/Breast Cancer
Chiron	DepoCyt	DepoCyt	Neoplastic Meningitis
Zeneca	ZD1839	ZD 1839	Non Small Cell Lung Cancer, Pancreatic Cancer
BASF	LU 79553	Bis-Naphtalimide	Oncology
BASF	LU 103793	Dolastain	Oncology
Schering Plough	Caetyx	Doxorubicin-Liposome	Ovarian/Breast Cancer
Lilly	Gemzar	Gemcitabine	Pancreatic Cancer, Non Small Cell Lung Cancer, Breast, Bladder and Ovarian
Zeneca	ZD 0473/Anormed	ZD 0473/Anormed	Platinum based NSCL, ovarian etc.
Yamanouchi	YM 116	YM 116	Prostate Cancer
Nycomed Amersham	Seeds/I-125 Rapid St	Iodine Seeds	Prostate Cancer
Agouron	Cdk4/cdk2 inhibitors	cdk4/cdk2 inhibitors	Solid Tumors

Marketer	Brand Name	Generic Name	Indication
Agouron	PARP inhibitors	PARP Inhibitors	Solid Tumors
Chiroscience	D4809	Dexifosamide	Solid Tumors
Bristol-Myers Squibb	UFT (Tegafur/Uracil)	UFT (Tegafur/Uracil)	Solid Tumors
Sankyo	Krestin	Krestin	Solid Tumors
Asta Medica	Ifex/Mesnex	Ifosamide	Solid Tumors
Bristol-Myers Squibb	Ifex/Mesnex	Ifosamide	Solid Tumors
Bristol-Myers Squibb	Vumon	Teniposide	Solid Tumors
Bristol-Myers Squibb	Paraplatin	Carboplatin	Solid Tumors
Bristol-Myers Squibb	Plantinol	Cisplatin, Stealth	Solid Tumors
Bristol-Myers Squibb	Plantinol	Cisplatin	Solid Tumors
Bristol-Myers Squibb	Vepeside	Etoposide	Solid Tumors Melanoma
Zeneca	ZD 9331	ZD 9331	Solid Tumors, Advanced Colorectal
Chugai	Taxotere	Docetaxel	Solid Tumors, Breast Cancer
Rhone Poulenc	Taxotere	Docetaxel	Solid Tumors, Breast Cancer
Glaxo Wellcome	Prodrug of guanine arabinside	prodrug of arabinside	T Cell Leukemia/Lymphoma & B Cell Neoplasm
Bristol-Myers Squibb	Taxane Analog	Taxane Analog	Taxol follow up

Another useful anti-cancer therapy is Interferon-α (e.g., INTRON® A, Schering).

The compounds useful according to the invention are nucleic acids. The nucleic acids may be double-stranded or single-stranded. Generally, double-stranded molecules may be more stable in vivo, while single-stranded molecules may have increased activity. The terms "nucleic acid" and "oligonucleotide" refer to multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)) or a modified base. As used herein, the terms refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base-containing polymer. The terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides with a covalently modified base and/or sugar. For example, they include nucleic acids having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include

sugars such as arabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have amino acid backbone with nucleic acid bases). In some embodiments the nucleic acids are homogeneous in backbone composition.

Nucleic acids also can include base analogs such as C-5 propyne modified bases. Wagner RW et al., *Nature Biotechnol* 14:840-4 (1996). Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, thymine, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

The nucleic acid is a linked polymer of bases or nucleotides. As used herein with respect to linked units of a nucleic acid, "linked" or "linkage" means two entities are bound to one another by any physicochemical means. Any linkage known to those of ordinary skill in the art, covalent or non-covalent, is embraced. Such linkages are well known to those of ordinary skill in the art. Natural linkages, which are those ordinarily found in nature connecting the individual units of a nucleic acid , are most common. The individual units of a nucleic acid may be linked, however, by synthetic or modified linkages.

Whenever a nucleic acid is represented by a sequence of letters it will be understood that the nucleotides are in 5' → 3' order from left to right and that "A" denotes adenosine, "C" denotes cytosine, "G" denotes guanosine, "T" denotes thymidine, and "U" denotes uracil unless otherwise noted.

Nucleic acid molecules useful according to the invention can be obtained from natural nucleic acid sources (e.g., genomic nuclear or mitochondrial DNA or cDNA), or are synthetic (e.g., produced by oligonucleotide synthesis). Nucleic acids isolated from existing nucleic acid sources are referred to herein as native, natural, or isolated nucleic acids. The nucleic acids useful according to the invention may be isolated from any source, including eukaryotic sources, prokaryotic sources, nuclear DNA, mitochondrial DNA, etc. Thus, the term nucleic acid encompasses both synthetic and isolated nucleic acids. The term "isolated" as used herein refers to a nucleic acid which is substantially free of other nucleic acids, proteins, lipids, carbohydrates or other materials with which it is naturally associated. The nucleic acids can be produced on a large scale in plasmids, (see Sambrook T et al., "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor Laboratory Press, New York, 1989) and separated into smaller pieces or administered whole. After being administered to a

subject the plasmid can be degraded into oligonucleotides. One skilled in the art can purify viral, bacterial, eukaryotic, etc., nucleic acids using standard techniques, such as those employing restriction enzymes, exonucleases or endonucleases.

For use in the instant invention, the nucleic acids can be synthesized de novo using any of a number of procedures well known in the art. For example, the b-cyanoethyl phosphoramidite method (Beaucage SL et al., *Tetrahedron Lett* 22:1859, 1981); nucleoside H-phosphonate method (Garegg et al., *Tetrahedron Lett* 27:4051-4, 1986; Froehler et al., *Nucl Acid Res* 14:5399-407, 1986; Garegg et al., *Tetrahedron Lett* 27:4055-8, 1986; Gaffney et al., *Tetrahedron Lett* 29:2619-22, 1988). These chemistries can be performed by a variety of automated oligonucleotide synthesizers available in the market.

In some embodiments, the nucleic acids useful according to the invention are immunostimulatory nucleic acids. An immunostimulatory nucleic acid is any nucleic acid, as described above, which is capable of modulating an immune response. A nucleic acid which modulates an immune response is one which produces any form of immune stimulation, including, but not limited to, induction of cytokines, B-cell activation, T-cell activation, monocyte activation. Immunostimulatory nucleic acids include, but are not limited to, CpG nucleic acids, methylated CpG nucleic acids, T-rich nucleic acids, poly-G nucleic acids, and nucleic acids having phosphate modified backbones, such as phosphorothioate backbones.

A "CpG nucleic acid" or a "CpG immunostimulatory nucleic acid" as used herein is a nucleic acid containing at least one unmethylated CpG dinucleotide (cytosine-guanine dinucleotide sequence, i.e., "CpG DNA" or DNA containing a 5' cytosine followed by 3' guanosine and linked by a phosphate bond) and activates a component of the immune system. The entire CpG nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5' CG 3' must be unmethylated.

In one embodiment the invention provides a CpG nucleic acid represented by at least the formula:

$$5'\ N_1X_1CGX_2N_2\ 3'$$

wherein X_1 and X_2 are nucleotides and N is any nucleotide and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N's each. In some embodiments X_1 is adenine, guanine, or thymine and X_2 is cytosine, adenine, or thymine. In other embodiments X_1 is cytosine and/or X_2 is guanine.

In other embodiments the CpG nucleic acid is represented by at least the formula:

$$5'\ N_1X_1X_2CGX_3X_4N_2\ 3'$$

wherein X_1, X_2, X_3, and X_4 are nucleotides. In some embodiments, X_1X_2 are nucleotides selected from the group consisting of: GpT, GpG, GpA, ApA, ApT, ApG, CpT, CpA, CpG, TpA, TpT, and TpG; and X_3X_4 are nucleotides selected from the group consisting of: TpT, CpT, ApT, TpG, ApG, CpG, TpC, ApC, CpC, TpA, ApA, and CpA; N is any nucleotide and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N's each. In some embodiments, X_1X_2 are GpA or GpT and X_3X_4 are TpT. In other embodiments X_1 or X_2 or both are purines and X_3 or X_4 or both are pyrimidines or X_1X_2 are GpA and X_3 or X_4 or both are pyrimidines.

In some embodiments N_1 and N_2 of the nucleic acid do not contain a CCGG or CGCG quadmer or more than one CCG or CGG trimer. The effect of a CCGG or CGCG quadmer or more than one CCG or CGG trimer depends in part on the status of the nucleic acid backbone. For instance, if the nucleic acid has a phosphodiester backbone or a chimeric backbone the inclusion of these sequences in the nucleic acid will only have minimal if any affect on the biological activity of the nucleic acid. If the backbone is completely phosphorothioate or significantly phosphorothioate then the inclusion of these sequences may have more influence on the biological activity or the kinetics of the biological activity, but compounds containing these sequences are still useful. In another embodiment the CpG nucleic acid has the sequence 5' $TCN_1TX_1X_2CGX_3X_4$ 3'.

A "T-rich nucleic acid" or "T-rich immunostimulatory nucleic acid" is a nucleic acid which includes at least one poly-T sequence and/or which has a nucleotide composition of greater than 25% T nucleotide residues and which activates a component of the immune system. A nucleic acid having a poly-T sequence includes at least four Ts in a row, such as 5' TTTT 3'. Preferably the T-rich nucleic acid includes more than one poly-T sequence. In preferred embodiments the T-rich nucleic acid may have 2, 3, 4, etc., poly-T sequences, such as oligonucleotide #2006 (5' TCGTCGTTTTGTCGTTTTGTCGTT 3', SEQ ID NO: 729). One of the most highly immunostimulatory T-rich oligonucleotides discovered according to the invention is a nucleic acid composed entirely of T nucleotide residues, e.g., oligonucleotide #2183 (5' TTTTTTTTTTTTTTTTTTTTTTTT 3', SEQ ID NO: 841). Other T-rich nucleic acids have a nucleotide composition of greater than 25% T nucleotide residues, but do not necessarily include a poly-T sequence. In these T-rich nucleic acids the T nucleotide resides may be separated from one another by other types of nucleotide residues,

i.e., G, C, and A. In some embodiments the T-rich nucleic acids have a nucleotide composition of greater than 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 99%, T nucleotide residues and every integer % in between. Preferably the T-rich nucleic acids have at least one poly-T sequence and a nucleotide composition of greater than 25% T nucleotide residues.

In one embodiment the T-rich nucleic acid is represented by at least the formula:

$$5'\ X_1X_2TTTTX_3X_4\ 3'$$

wherein X_1, X_2, X_3, and X_4 are nucleotides. In one embodiment X_1X_2 is TT and/or X_3X_4 is TT. In another embodiment X_1X_2 are any one of the following nucleotides TA, TG, TC, AT, AA, AG, AC, CT, CC, CA, CG, GT, GG, GA, and GC; and X_3X_4 are any one of the following nucleotides TA, TG, TC, AT, AA, AG, AC, CT, CC, CA, CG, GT, GG, GA, and GC.

In some embodiments it is preferred that the T-rich nucleic acid does not contain poly-C (CCCC), poly-A (AAAA), poly-G (GGGG), CpG motifs, or multiple GGs. In other embodiments the T-rich nucleic acid includes these motifs. Thus in some embodiments of the invention the T-rich nucleic acids include CpG dinucleotides and in other embodiments the T-rich nucleic acids are free of CpG dinucleotides. The CpG dinucleotides may be methylated or unmethylated.

Poly-G containing nucleic acids are also immunostimulatory. A variety of references, including Pisetsky DS et al., *Mol Biol Rep* 18:217-21 (1993); Krieger M et al., *Annu Rev Biochem* 63:601-37 (1994); Macaya RF et al., *Proc Natl Acad Sci USA* 90:3745-9 (1993); Wyatt JR et al., *Proc Natl Acad Sci USA* 91:1356-60 (1994); Rando and Hogan, 1998, In: Applied Antisense Oligonucleotide Technology, eds. Krieg AM and Stein C, pp. 335-352; and Kimura Y et al., *J Biochem (Tokyo)* 116:991-4 (1994) also describe the immunostimulatory properties of poly-G nucleic acids.

Poly G nucleic acids preferably are nucleic acids having the following formulas:

$$5'\ X_1X_2GGGX_3X_4\ 3'$$

wherein X_1, X_2, X_3, and X_4 are nucleotides. In preferred embodiments at least one of X_3 and X_4 are a G. In other embodiments both of X_3 and X_4 are a G. In yet other embodiments the preferred formula is 5' GGGNGGG 3', or 5' GGGNGGGNGGG 3' wherein N represents between 0 and 20 nucleotides. In other embodiments the poly-G nucleic acid is free of unmethylated CG dinucleotides, such as, for example, the nucleic acids listed in Table 4 below as SEQ ID NOs: 12-14, 23, 56, 100, 155, 163, 182, 227, 237, 246, 400, 407, 429, 430,

432, 435, 438, 439, 446, 450, 451, 480, 487, 493, 522, 661, 662, 671-673, 807, 808, 821, 823, and 834. In other embodiments the poly-G nucleic acid includes at least one unmethylated CG dinucleotide, such as, for example, the nucleic acids listed in Table 4 below as SEQ ID NOs: 6, 7, 22, 26, 28-30, 87, 115, 141, 177, 191, 209, 254, 258, 267, 303, 317, 329, 335, 344, 345, 395, 414, 417, 418, 423-426, 428, 431, 433, 434, 436, 437, 440, 442-445, 447-449, 458, 460, 463, 467-469, 474, 515, 516, 594, 638-640, 663, 664, 727, 752, 776, 795, 799, 817, 818, 831, and 832.

Nucleic acids having modified backbones, such as phosphorothioate backbones, also fall within the class of immunostimulatory nucleic acids. U.S. Patents Nos. 5,723,335 and 5,663,153 issued to Hutcherson, et al. and related PCT publication WO95/26204 describe immune stimulation using phosphorothioate oligonucleotide analogues. These patents describe the ability of the phosphorothioate backbone to stimulate an immune response in a non-sequence specific manner.

The immunostimulatory nucleic acids may be any size but in some embodiments are in the range of between 6 and 100 or in some embodiments between 8 and 35 nucleotides in size. Immunostimulatory nucleic acids can be produced on a large scale in plasmids. These may be administered in plasmid form or alternatively they can be degraded into oligonucleotides.

"Palindromic sequence" shall mean an inverted repeat (i.e., a sequence such as ABCDEE'D'C'B'A' in which A and A' are bases capable of forming the usual Watson-Crick base pairs and which includes at least 6 nucleotides in the palindrome. In vivo, such sequences may form double-stranded structures. In one embodiment the nucleic acid contains a palindromic sequence. In some embodiments when the nucleic acid is a CpG nucleic acid, a palindromic sequence used in this context refers to a palindrome in which the CpG is part of the palindrome, and optionally is the center of the palindrome. In another embodiment the nucleic acid is free of a palindrome. A nucleic acid that is free of a palindrome does not have any regions of 6 nucleotides or greater in length which are palindromic. A nucleic acid that is free of a palindrome can include a region of less than 6 nucleotides which are palindromic.

A "stabilized nucleic acid molecule" shall mean a nucleic acid molecule that is relatively resistant to in vivo degradation (e.g., via an exonuclease or endonuclease). Stabilization can be a function of length or secondary structure. Nucleic acids that are tens to

hundreds of kbs long are relatively resistant to in vivo degradation. For shorter nucleic acids, secondary structure can stabilize and increase their effect. For example, if the 3' end of an oligonucleotide has self-complementarity to an upstream region, so that it can fold back and form a sort of stem loop structure, then the oligonucleotide becomes stabilized and therefore exhibits more activity.

Some stabilized oligonucleotides of the instant invention have a modified backbone. It has been demonstrated that modification of the oligonucleotide backbone provides enhanced activity of the nucleic acids when administered in vivo. Nucleic acids, including at least two phosphorothioate linkages at the 5' end of the oligonucleotide and multiple phosphorothioate linkages at the 3' end, preferably 5, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases. Other modified oligonucleotides include phosphodiester modified oligonucleotide, combinations of phosphodiester and phosphorothioate oligonucleotide, methylphosphonate, methylphosphorothioate, phosphorodithioate, and combinations thereof. Each of these combinations and their particular effects on immune cells is discussed in more detail in PCT Published Patent Application WO98/18810 claiming priority to U.S. Serial Nos. 08/738,652 (now issued as U.S. Patent No. 6,207,646 B1) and 08/960,774 (now issued as U.S. Patent No. 6,239,116 B1), filed on October 30, 1996 and October 30, 1997 respectively, the entire contents of which is hereby incorporated by reference. It is believed that these modified oligonucleotides may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization. Both phosphorothioate and phosphodiester nucleic acids are active in immune cells.

Other stabilized oligonucleotides include: nonionic DNA analogs, such as alkyl- and aryl-phosphates (in which the charged phosphonate oxygen is replaced by an alkyl or aryl group), phosphodiester and alkylphosphotriesters, in which the charged oxygen moiety is alkylated. Oligonucleotides which contain diol, such as tetraethyleneglycol or hexaethyleneglycol, at either or both termini have also been shown to be substantially resistant to nuclease degradation.

For use in vivo, nucleic acids are preferably relatively resistant to degradation (e.g., via endonucleases and exonucleases). Secondary structures, such as stem loops, can stabilize nucleic acids against degradation. Alternatively, nucleic acid stabilization can be accomplished via phosphate backbone modifications. One type of stabilized nucleic acid has

at least a partial phosphorothioate modified backbone. Phosphorothioates may be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Patent No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Patent No. 5,023,243 and European Patent No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described. Uhlmann E et al., *Chem Rev* 90:544-84 (1990); Goodchild J, *Bioconjugate Chem* 1:165-87 (1990).

The immunostimulatory nucleic acids having backbone modifications useful according to the invention in some embodiments are S- or R-chiral immunostimulatory nucleic acids. An "S chiral immunostimulatory nucleic acid" as used herein is an immunostimulatory nucleic acid wherein at least two nucleotides have a backbone modification forming a chiral center and wherein a plurality of the chiral centers have S chirality. An "R chiral immunostimulatory nucleic acid" as used herein is an immunostimulatory nucleic acid wherein at least two nucleotides have a backbone modification forming a chiral center and wherein a plurality of the chiral centers have R chirality. The backbone modification may be any type of modification that forms a chiral center. The modifications include but are not limited to phosphorothioate, methylphosphonate, methylphosphorothioate, phosphorodithioate, 2'-OMe and combinations thereof. In other embodiments they are non-chiral. A non-chiral nucleic acid is any nucleic acid which does not have at least two chiral centers.

The chiral immunostimulatory nucleic acids must have at least two nucleotides within the nucleic acid that have a backbone modification. All or less than all of the nucleotides in the nucleic acid, however, may have a modified backbone. Of the nucleotides having a modified backbone (referred to as chiral centers), a plurality have a single chirality, S or R. A "plurality" as used herein refers to an amount greater than or equal to 75%. Thus, less than all of the chiral centers may have S or R chirality as long as a plurality of the chiral centers have S or R chirality. In some embodiments at least 75%, 80%, 85%, 90%, 95%, or 100% of the chiral centers have S or R chirality. In other embodiments at least 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides have backbone modifications.

The S- and R- chiral immunostimulatory nucleic acids may be prepared by any method known in the art for producing chirally pure oligonucleotides. Stec et al. teach methods for producing stereopure phosphorothioate oligodeoxynucleotides using an oxathiaphospholane. Stec WJ et al., *J Am Chem Soc* 117:12019 (1995). Other methods for making chirally pure oligonucleotides have been described by companies such as ISIS Pharmaceuticals. U.S. Patents which disclose methods for generating stereopure oligonucleotides include 5,212,295, 5,359,052, 5,506,212, 5,512,668, 5,521,302, 5,599,797, 5,837,856, 5,856,465, and 5,883,237, each of which is hereby incorporated by reference in its entirety.

Other sources of nucleic acids useful according to the invention include standard viral and bacterial vectors, many of which are commercially available. In its broadest sense, a "vector" is any nucleic acid material which is ordinarily used to deliver and facilitate the transfer of nucleic acids to cells. The vector as used herein may be an empty vector or a vector carrying a gene which can be expressed. In the case when the vector is carrying a gene the vector generally transports the gene to the target cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In this case the vector optionally includes gene expression sequences to enhance expression of the gene in target cells such as immune cells, but it is not required that the gene be expressed in the cell.

In general, vectors include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources. Viral vectors are one type of vector and include, but are not limited to, nucleic acid sequences from the following viruses: retrovirus, such as Moloney murine leukemia virus, Harvey murine sarcoma virus, murine mammary tumor virus, and Rous sarcoma virus; adenovirus, adeno-associated virus; SV40-type viruses; polyoma viruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known to the art. Some viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with a nucleic acid to be delivered. Non-cytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA.

Standard protocols for producing empty vectors or vectors carrying genes (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a

packaging cell lined with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and/or infection of the target cells with viral particles) are provided in Kriegler M, "Gene Transfer and Expression, A Laboratory Manual," W.H. Freeman Co., New York (1990) and Murry EJ, Ed., "Methods in Molecular Biology," vol. 7, Humana Press, Inc., Cliffton, New Jersey (1991).

Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well-known to those of skill in the art. See e.g., Sambrook et al., "Molecular Cloning: A Laboratory Manual," Second Edition, Cold Spring Harbor Laboratory Press, 1989. In the last few years, plasmid vectors have been found to be particularly advantageous for delivering genes to cells in vivo because of their inability to replicate within and integrate into a host genome. Some plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operatively encoded within the plasmid. Some commonly used plasmids include pBR322, pUC18, pUC19, pcDNA3.1, pSV40, and pBlueScript. Other plasmids are well-known to those of ordinary skill in the art. Additionally, plasmids may be custom designed using restriction enzymes and ligation reactions to remove and add specific fragments of DNA.

It has recently been discovered that plasmids (empty or gene-carrying) can be delivered to the immune system using bacteria. Modified forms of bacteria such as *Salmonella* can be transfected with the plasmid and used as delivery vehicles. The bacterial delivery vehicles can be administered to a host subject orally or by other administration means. The bacteria deliver the plasmid to immune cells, e.g., dendritic cells, probably by passing through the gut barrier. High levels of immune protection have been established using this methodology. Such methods of delivery are useful for the aspects of the invention utilizing systemic delivery of nucleic acid.

As used herein, administration of an immunostimulatory nucleic acid is intended to embrace the administration of one or more immunostimulatory nucleic acids which may or may not differ in terms of their profile, sequence, backbone modifications and biological effect. As an example, CpG nucleic acids and T-rich nucleic acids may be administered to a single subject along with an antibody and optionally a cancer therapy. In another example, a plurality of CpG nucleic acids which differ in nucleotide sequence may also be administered to a subject.

Some of the nucleic acids useful according to the invention and described herein are presented in Table 4 below.

Table 4: Exemplary Nucleic Acids.

SEQUENCE	BACKBONE	SEQ ID NO:
aaaaaa	s	1
aaaaaaaaaaaaaaaaaaaa	o	2
aaaaaccccccccccaaaaa	o	3
aaaacatgacgttcaaaaaa	sos	4
aaaacatgacgttcaaaaaa	s2	5
aaaacatgacgttcgggggg	sos	6
aaaacatgacgttcgggggg	s2	7
aaaacgtt	o	8
aaaatcaacgttgaaaaaaa	sos	9
aaaatctgtgcttttaaaaaa	sos	10
aaaattgacgttttaaaaaa	sos	11
aaacattctggggaattttaagaagtaaacat	o	12
aaacattctggggaattttaagaagttcctccctcccc	o	13
aaacattctggggaattttgtctagtaaacat	o	14
aacgctcgaccttcgat	o	15
aacgctggaccttccat	o	16
aacgctggaccttccatgtc	sos	17
aacgtt	o	18
aacgttct	o	19
aacgttg	s	20
aacgttga	o	21
aacgttgaggggcat	o	22
aaggtggggcagtctcaggga		23
aatagtcgccataacaaaac	o	24
aatagtcgccatcccccccc	o	25
aatagtcgccatcccgggac	o	26
aatagtcgccatcgcgcgac	o	27
aatagtcgccatggcggggc	o	28
aattctctatcggggcttctgtgtctgttgctggttccgctttat	o	29
acaaccacgagaacgggaac		30
acaacgtt	o	31
acaacgttga	o	32
accacaacgagaggaacgca		33
accatcctgaggccattcgg		34
accatggacgaactgtttcccctc	s	35
accatggacgacctgtttcccctc	s	36
accatggacgagctgtttcccctc	s	37
accatggacgagctgtttcccctc		38
accatggacgatctgtttcccctc	s	39
accatggacggtctgtttcccctc	s	40
accatggacgtactgtttcccctc	s	41
accatggacgttctgtttcccctc	s	42
acccatcaatagctctgtgc	s	43
acccgtcgtaattatagtaaaaccc	o	44
accgcatggattctaggcca	s	45
accttattaagattgtgcaatgtgacgtcctttagcatcgcaaga	o	46
acgctggaccttccat		47
acgtcgttcccccccccccc	o	48

SEQUENCE	BACKBONE	SEQ ID NO:
acgtgt	s	49
actagacgttagtgtga	o	50
actagacgttagtgtga	s	51
actggacgttagcgtga	o	52
acttctcatagtccctttggtccag	o	53
agaacgtt	o	54
agacagacacgaaacgaccg		55
agactcatgggaaaatcccacatttga	o	56
agatagcaaatcggctgacg	o	57
agatggttctcagataaagcggaa		58
agcaccgaacgtgagagg	o	59
agcacggtagccttccta		60
agcagctttagagctttagagctt	s	61
agcatcaggaacgacatgga	o	62
agcatcaggaccgacatgga	o	63
agcgctga	o	64
agctcaacgtcatgc	o	65
agctccatggtgctcactg	s	66
aggatatc	o	67
aggtacagccaggactacga		68
agicccgigaacgiattcac	o	69
agtgactctccagcgttctc	o	70
agtgcgattcgagatcg	o	71
agtgcgattgcagatcg	o	72
agtgct	s	73
agtgct	o	74
agttgcaact	o	75
ataaagcgaaactagcagcagtttc	o	76
ataacgtt	o	77
ataatagagcttcaagcaag	s	78
ataatccagcttgaaccaag	s	79
ataatcgacgttcaagcaag	s	80
ataatcgacgttcccccccc	s	81
ataatcgtcgttcaagcaag	s	82
ataatcgtgcgttcaagaaag	s	83
atagacaaaaattccctccccggagcc	o	84
atatatatatatatatat	s	85
atatctaatcaaaacattaacaaa	o	86
atcaggaacgtcatgggaagc	o	87
atcgacctacgtgcgttctc	o	88
atcgacctacgtgcgttztc	o	89
atcgactcgagcgttctc	o	90
atcgactctcgagcgttctc	o	91
atcgactctcgagcgttctc	sos	92
atcgactctcgagtgttctc	o	93
atcgactctcgagzgttctc	o	94
atcgactctctcgagcgttctc	o	95
atcgacttcgagcgttctc	o	96
atcgatcgagcgttctc	o	97
atcgatgt	o	98
atcggaggactggcgcgccg		99
atctggtgagggcaagctatg	s	100
atgacgttcctgacgtt	s	101
atgcactctgcagcgttctc	o	102
atgcatgt	o	103

SEQUENCE	BACKBONE	SEQ ID NO:
atgcccctcaacgtt	o	104
atgctaaaggacgtcacattgca	o	105
atggaaggtccacgttctc	o	106
atggaaggtccagcgttct	o	107
atggaaggtccagcgttctc	o	108
atggaaggtccagtgttctc	o	109
atggaaggtcgagcgttctc	o	110
atggactctccagcgttctc	o	111
atgtcctcggtcctgatgct	o	112
atgtttactagacaaaattcccccagaatgttt	o	113
atgtttacttcttaaaattcccccagaatgttt	o	114
attcgatcggggcggggcgag	o	115
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tzgtggttcccccccccccc	o	846
tzgtzgttttgtzgttttgtzgtt	o	847
tzgtzgttttgtzgttttgtzgtt	s	848

In Table 4 with respect to sequences the letter symbols aside from a, c, t, and g are defined as follows: "b" indicates a biotin moiety attached to that end of the oligonucleotide when it is single and is listed on the 5' or 3' end of oligonucleotide; "d" represents a, g, or t; "f" represents fluorescein isothiocyanate (FITC) moiety attached to the 5' or 3' end of oligonucleotide; "h" represents a, c, or t; "i" represents inosine; "n" represents any nucleotide; "z" represents 5-methylcytosine.

Also in Table 4 with respect to backbones the notations are defined as follows: "o" represents phosphodiester; "os" represents phosphorothioate and phosphodiester chimeric with phosphodiester on 5' end; "os2" represents phosphorodithioate and phosphodiester chimeric with phosphodiester on 5' end; "p-ethoxy" represents p-ethoxy backbone (see, e.g., U.S. Patent No. 6,015,886); "po" represents phosphodiester; "s" represents phosphorothioate; "s2" represents phosphorodithioate; "s2o" represents phosphorodithioate and phosphodiester chimeric with phosphodiester on 3' end; "so" represents phosphorothioate and phosphodiester

chimeric with phosphodiester on 3' end; and "sos" represents chimeric phosphorothioate/phosphodiester with phosphorothioate at the 5' and 3' ends.

The nucleic acids are delivered in effective amounts. The term "effective amount" of a immunostimulatory nucleic acid refers to the amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of an immunostimulatory nucleic acid could be that amount necessary to cause activation of the immune system. According to some aspects of the invention, an effective amount is that amount of an immunostimulatory nucleic acid and that amount of an antibody, which when combined or co-administered, results in the prevention or the treatment of the cancer. In some embodiments a synergistic effect is observed. A synergistic amount is that amount which produces an anti-cancer response that is greater than the sum of the individual effects of either the immunostimulatory nucleic acid and the antibody alone. For example, a synergistic combination of an immunostimulatory nucleic acid and an antibody provides a biological effect which is greater than the combined biological effect which could have been achieved using each of the components (i.e., the nucleic acid and the antibody) separately. The biological effect may be the amelioration and or absolute elimination of symptoms resulting from the cancer. In another embodiment, the biological effect is the complete abrogation of the cancer, as evidenced for example, by the absence of a tumor or a biopsy or blood smear which is free of cancer cells.

The effective amount of immunostimulatory nucleic acid necessary to treat a cancer or in the reduction of the risk of developing a cancer may vary depending upon the sequence of the immunostimulatory nucleic acid, the backbone constituents of the nucleic acid, and the mode of delivery of the nucleic acid. The effective amount for any particular application can also vary depending on such factors as the cancer being treated, the particular immunostimulatory nucleic acid being administered (e.g., the nature, number or location of immunostimulatory motifs in the nucleic acid), the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular immunostimulatory nucleic acid and antibody combination without necessitating undue experimentation. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned

which does not cause substantial toxicity and yet is entirely effective to treat the particular subject.

Therapeutic doses of cancer therapies are well known in the field of medicine for the treatment of cancer. These dosages have been extensively described in references such as Remington's Pharmaceutical Sciences, 18th ed., 1990; as well as many other medical references relied upon by the medical profession as guidance for the treatment of cancer. Therapeutic dosages of immunostimulatory nucleic acids have also been described in the art and methods for identifying therapeutic dosages in subjects are described in more detail herein.

Subject doses of the compounds described herein typically range from about 0.1 μg to 10 mg per administration, which depending on the application could be given daily, weekly, or monthly and any other amount of time therebetween. More typically mucosal or local doses range from about 10 μg to 5 mg per administration, and most typically from about 100 μg to 1 mg, with 2 - 4 administrations being spaced hours, days or weeks apart. More typically, immune stimulant doses range from 1 μg to 10 mg per administration, and most typically 10 μg to 1 mg, with daily or weekly administrations. Subject doses of the compounds described herein for parenteral delivery, wherein the compounds are delivered without another therapeutic agent are typically 5 to 10,000 times higher than the effective mucosal dose or for immune stimulant applications, and more typically 10 to 1,000 times higher, and most typically 20 to 100 times higher. More typically parenteral doses for these purposes range from about 10 μg to 5 mg per administration, and most typically from about 100 μg to 1 mg, with 2 - 4 administrations being spaced hours, days or weeks apart. In some embodiments, however, parenteral doses for these purposes may be used in a range of 5 to 10,000 times higher than the typical doses described above.

For any compound described herein the therapeutically effective amount can be initially determined from animal models, e.g., the animal models described herein. A therapeutically effective dose can also be determined from human data for CpG nucleic acids which have been tested in humans (human clinical trials have been initiated and the results publicly disseminated) and for compounds which are known to exhibit similar pharmacological activities. Higher doses may be required for parenteral administration, as described above. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy

based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

The formulations of the invention are administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of the nucleic acid can be administered to a subject by any mode that delivers the nucleic acid to a subject. "Administering" the pharmaceutical composition of the present invention may be accomplished by any means known to the skilled artisan. Some routes of administration include but are not limited to oral, intranasal, intratracheal, inhalation, ocular, vaginal, rectal, parenteral (e.g., intramuscular, intradermal, intravenous or subcutaneous injection) and direct injection.

For oral administration, the compounds (i.e., nucleic acids and antibodies) can be delivered alone without any pharmaceutical carriers or formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. The term "pharmaceutically-acceptable carrier" means one or more compatible solid or liquid filler, dilutants or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or

alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers for neutralizing internal acid conditions.

Dragee cores may be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray, from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as

suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions may also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries

such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of present methods for drug delivery, see Langer R, *Science* 249:1527-33 (1990), which is incorporated herein by reference.

The nucleic acids and/or antibodies may be administered per se (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

The nucleic acids or other therapeutics useful in the invention may be delivered in mixtures with additional antibodies. A mixture may consist of several antibodies in addition to the nucleic acid.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular nucleic acids or antibodies selected, the particular condition being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of an immune response without causing clinically unacceptable adverse effects. Preferred modes of administration are discussed above.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately

bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product. Liquid dose units are vials or ampoules. Solid dose units are tablets, capsules and suppositories.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the compounds, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Patent No. 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di-, and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the invention is contained in a form within a matrix such as those described in U.S. Patent Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

The nucleic acid may be directly administered to the subject or may be administered in conjunction with a pharmaceutically acceptable carrier or a delivery vehicle. The nucleic acid and optionally other therapeutic agents may be administered alone (e.g., in saline or buffer) or using any delivery vehicles known in the art. One type of delivery vehicle is referred to herein as a nucleic acid delivery complex. A "nucleic acid delivery complex" shall mean a nucleic acid molecule associated with (e.g., ionically or covalently bound to; or encapsulated within) a targeting means (e.g., a molecule that results in higher affinity binding to target cell (e.g., dendritic cell surfaces and/or increased cellular uptake by target cells). Examples of nucleic acid delivery complexes include nucleic acids associated with: a sterol (e.g., cholesterol), a lipid (e.g., a cationic lipid, virosome or liposome), or a target cell specific binding agent (e.g., a ligand recognized by target cell specific receptor). Preferred

complexes may be sufficiently stable in vivo to reduce significant uncoupling prior to internalization by the target cell. However, the complex may be cleavable under appropriate conditions within the cell so that the nucleic acid may be released in a functional form.

The nucleic acids may be delivered by non-invasive methods as described above. Non-invasive delivery of compounds is desirable for treatment of children, elderly, animals, and even adults and also to avoid the risk of needle-stick injury. Delivery vehicles for delivering compounds to mucosal surfaces have been described and include but are not limited to: Cochleates (Gould-Fogerite et al., 1994, 1996); Emulsomes (Vancott et al., 1998, Lowell et al., 1997); ISCOMs (Mowat et al., 1993, Carlsson et al., 1991, Hu et al., 1998, Morein et al., 1999); Liposomes (Childers et al., 1999, Michalek et al., 1989, 1992, de Haan 1995a, 1995b); Live bacterial vectors (e.g., *Salmonella, Escherichia coli, Bacillus Calmette-Guérin, Shigella, Lactobacillus*) (Hone et al., 1996, Pouwels et al., 1998, Chatfield et al., 1993, Stover et al., 1991, Nugent et al., 1998); Live viral vectors (e.g., Vaccinia, adenovirus, Herpes Simplex) (Gallichan et al., 1993, 1995, Moss et al., 1996, Nugent et al., 1998, Flexner et al., 1988, Morrow et al., 1999); Microspheres (Gupta et al., 1998, Jones et al., 1996, Maloy et al., *1994*, Moore et al., *1995*, O'Hagan et al., *1994*, Eldridge et al., *1989*); nucleic acid vaccines (Fynan et al., 1993, Kuklin et al., 1997, Sasaki et al., 1998, Okada et al., 1997, Ishii et al., 1997); Polymers (e.g., carboxymethylcellulose, chitosan) (Hamajima et al., 1998, Jabbal-Gill et al., 1998); Polymer rings (Wyatt et al., 1998); Proteosomes (Vancott et al., 1998, Lowell et al., 1988, *1996, 1997*); Sodium Fluoride (Hashi et al., 1998); Transgenic plants (Tacket et al., 1998, Mason et al., 1998, Haq et al., 1995); Virosomes (Gluck et al., 1992, Mengiardi et al., 1995, Cryz et al., 1998); Virus-like particles (Jiang et al., 1999, Leibl et al., 1998).

The invention also includes kits. The kits generally include a package with a plurality of containers housing active agents and instructions for carrying out the methods of the invention. The active agents include but are not limited to immunostimulatory nucleic acids, antibodies such as antibodies specific for a cell surface antigen, and anti-cancer therapies.

The following examples are provided to illustrate specific instances of the practice of the present invention and are not to be construed as limiting the present invention to these examples. As will be apparent to one of ordinary skill in the art, the present invention will find application in a variety of compositions and methods.

Examples

Introduction:

Extensive cross-talk exists between healthy B cells and T cells. There is evidence that malignant B cells also communicate with T cells. However, malignant cells appear to differ from their normal counterparts in a number of ways, including a decreased tendency to undergo apoptosis in response to normal signals, altered expression of a variety of surface markers, and altered ability to function as effective antigen presenting cells. Lagneaux L et al., *Blood* 91:2387-96 (1998); Gordon J et al., *Leukemia* 7 Suppl 2:S5-9 (1993); Gordon J et al., *Adv Exp Med Biol* 406:139-44 (1996); Chaperot L et al., *Exp Hematol* 27:479-88 (1999). Immunotherapeutic approaches have recently become part of our therapy of some subtypes of B-cell malignancy. Improved immunotherapy of B-cell malignancy will need to be designed based on the growing understanding of the cellular immunology of this disease. Schultze JL et al., *J Mol Med* 77:322-32 (1999).

A variety of cellular receptors and antigens are involved in growth, differentiation and apoptosis of B-cell malignancies. Antibodies or ligands against a variety of antigens can cause growth inhibition or even apoptosis including CD20, surface immunoglobulins, MHC II, CD80, CD86 and CD40. Maloney DG, *Semin Oncol* 26:74-8 (1999); McLaughlin P et al., *Semin Oncol* 26:79-87 (1999); Shan D et al., *Blood* 91:1644-52 (1998); Coiffier B et al., *Blood* 92:1927-32 (1998); McLaughlin P et al., *Oncology (Huntingt)* 12:1763-70, 1775-7 (1998); Tutt AL et al., *J Immunol* 161:3176-85 (1998); Funakoshi S et al., *Blood* 83:2787-94 (1994); Mayumi M et al., *J Allergy Clin Immunol* 98:S238-47 (1996); Higaki Y et al., *Immunol Cell Biol* 72:205-14 (1994); Elsasser D et al., *Blood* 87:3803-12 (1996); Link BK et al., *Blood* 81:3343-9 (1993); Link BK et al., *Int J Cancer* 77:251-6 (1998). The relative contribution of antibody dependent cellular cytotoxicity (ADCC) versus trans-membrane signaling mediated by anti-B cell antibodies remains unclear. In the present study, we examined how CpG-DNA impacts on the phenotype, apoptosis and proliferation of different types of B-cell malignancy including follicular B-cell lymphoma and B-CLL.

Materials and Methods:

Cell culture: Fresh lymph node samples were obtained from the operating suite and were minced with a scalpel under aseptic conditions. The resulting suspension was passed sequentially through a sterilized sieve-tissue grinder containing a nylon mesh screen, a 150 μm mesh screen and a 60 μm mesh screen. Alternatively, mononuclear cells were obtained

from peripheral blood or pleural fluid as described. Hartmann G et al., *J Pharmacol Exp Ther* 285:920-8 (1998). Red blood cells were removed by resuspending the cells in 5 ml ACK lysis buffer according to standard procedures. Cells were frozen slowly and stored in liquid nitrogen. For analysis, cells were thawed and resuspended in 10 % (v/v) heat-inactivated (56°C, 1 h) FCS (HyClone, Logan, UT), 1.5 mM L-glutamine (all from Gibco BRL, Grand Island, NY) and incubated on a 96-well-plate (1 x 10^6 cells/ml) in the presence of ODN as indicated below. Not all assays were performed for all samples because of the limited number of cells available for some samples.

Oligonucleotides: Nuclease-resistant phosphorothioate-modified oligodeoxynucleotide (ODN) were purchased from Operon Technologies (Alameda, CA) and Hybridon Specialty Products (Milford, MA). Sequences were as follows: CpG ODN 2006: 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO: 729), and control ODN 2017: 5'-CCCCCCCCCCCCCCCCCCCC-3' (SEQ ID NO: 168). ODN was diluted in TE (10 mM Tris-HCl, 1 mM EDTA, pH 8) using pyrogen-free reagents. ODN was added at a final concentration of 5 μg/ml.

Flow cytometry: Cells were washed and resuspended in ice-cold PBS or Annexin V binding buffer (10 mM HEPES/NaOH, 140 mM NaCl, 2.5 mM $CaCl_2$, pH 7.4). Murine or human serum was added (final concentration 1%) to block non-specific binding of antibodies. Surface antigen staining was performed as described. Hartmann G et al., *J Pharmacol Exp Ther* 285:920-8 (1998). In brief, 1 x 10^5 cells per sample were stained with CyChrome-labeled anti-CD19 and FITC- or PE-labeled antibodies as indicated for 20 min on ice. They were then washed and analyzed by flow cytometry. Monoclonal antibodies to CD40 (5C3), CD69 (FN50), CD80 (L307.4), CD86 (IT2.2), CD54 (HA58), MHC I (G46-2.6) and MHC II (TU39) as well as isotype controls (IgG1, MOPC-21 and IgG2a, G155-178) were purchased from PharMingen, San Diego, CA. FITC-labeled polyclonal anti-human Ig was purchased from Southern Biotech, Birmingham, AL. 1D10, a monoclonal humanized antibody directed against a variant of HLA-DR was produced in our laboratory as described earlier. Link BK et al., *Blood* 81:3343-9 (1993). C2B8, a monoclonal humanized anti-CD20 antibody, was purchased from IDEC Pharmaceuticals, San Diego, CA. 1D10 and C2B8 were labeled with FITC according to standard protocols. The analysis gate was set on viable cells identified according to FSC/SSC characteristics and Annexin V staining (> 97 % viable cells within analysis gate). Spectral overlap was corrected by appropriate compensation. Flow

cytometric data from 1 x 10^4 cells per sample were acquired on a FACScan (Beckton Dickinson Immunocytometry Systems, San Jose, CA). Data were analyzed using the computer program FlowJo (version 2.5.1, Tree Star, Inc., Stanford, CA).

CFSE staining: CFSE 5- (and 6-) carboxyfluorescein diacetate succinimidyl ester, Molecular Probes, USA, is a fluorescein-derived intracellular fluorescent label which is divided equally between daughter cells upon cell division. Staining of cells with CFSE allows both quantification and immunophenotyping of proliferating cells in a mixed cell suspension. Interference between oligonucleotide degradation products and thymidine uptake (standard proliferation assay) is avoided by using this method. The technique has described in detail previously. Lyons AB et al., *J Immunol Methods* 171:131-7 (1994). Briefly, cells were washed twice in PBS, resuspended in PBS (1 x 10^7 cells/ml) containing CFSE at a final concentration of 1 μM, and incubated at 37°C for 10 minutes. Cells were washed three times with PBS.

TUNEL assay: A two-color DNA strand break labeling assay, based on a modification of the assay described by Li et al. (Li X et al., *ExpCell Res* 222:28-37 (1996)) was used to assess B-cell proliferation in response to CpG ODN. This assay involved terminal transferase-mediated dUTP nick end labeling (TUNEL) before and after induction of DNA strand breaks in BrdU-labeled cells. Briefly, cells were cultured for 3 days with and without ODN. They were then incubated for 16 hours in 10μM BrdU and placed onto slides by cytospin. Cells were then in 1% paraformaldehyde in PBS for 15 minutes followed by 20 minutes in 70% ethanol. DNA cleavage indicative of apoptosis cells was detected by labeling the 3'-DNA end of nicked strands with FITC-ddUTP (Boehringer-Mannheim). The use of dideoxy-dUTP prevented further elongation of the 3'-ends in subsequent steps. Slides were then placed face-down on a 2mm support at both ends on a UV transilluminator and exposed for 5 minutes. The new DNA strand breaks induced by photolysis at sites of BrdU incorporation (i.e., proliferating cells) were detected by a second TUNEL labeling using tetramethylrhodamine-dUTP (TMR-dUTP, Boehringer-Mannheim). Both TUNEL staining steps included incubating slides in 50μl of TdT mix (34μl distilled water, 10μl of 5X TdT buffer, 5μl of 25mM cobalt chloride, 12.5 units terminal transferase and 0.5nmol fluorochrome-conjugated-dUTP) (Boehringer-Mannheim) under a coverslip for one hour at 37°C in a humidified chamber. The slides were then washed in 5 quick changes of distilled water followed by 3 changes of 2XSSC containing 30% formamide for 5 minutes each at

room temperature. After the second TUNEL labeling step, cells were counterstained for CD19, and also stained with Wright solution for blood cell differentiation and mounted in Vectashield media containing DAPI counterstain (Vector Laboratories, Burlingame, CA). The morphology and staining of cells were assessed using both visible light and fluorescence microscopy. Apoptotic cells were identified by green fluorescence (FITC label), and proliferating cells by red fluorescence (TMR label). The percentage of apoptotic and proliferating cells was determined by counting at least 200 cells per sample by three observers blinded to whether cells were treated with ODN. Mean and standard error were determined for each sample based on these three readings.

Example 1: Immunostimulatory nucleic acids induce morphological and phenotypic changes in malignant B cells.

Our prior studies demonstrated that activation of naive human B cells by CpG ODN results in increased cell size (FSC) and granularity (SSC). Hartmann G et al., *J Immunol* 164:944-53 (2000). We therefore first determined whether such changes also occur in malignant B cells. Primary malignant B cells were obtained from lymph node biopsies, peripheral blood, or pleural fluid of patients with various types of B-cell malignancy. In addition, cells from the lymph node of a patient with benign reactive follicular hyperplasia were studied. Nine samples in total were evaluated (see Table 5). Cells were incubated for 72 hours in media containing CpG ODN 2006 (5 μg/ml) or control ODN 2017. FSC and SSC were examined with gating on CD19+ viable cells (**Figure 1**). Varying degrees of change in FSC and SSC were noted in response to CpG ODN 2006 when compared to control ODN 2017 or medium alone. Comparable changes were not found in the cells from the patient with benign reactive follicular hyperplasia.

Figure 1 depicts the morphologic changes of marginal zone lymphoma cells upon CpG ODN stimulation. Malignant B cells from a patient with marginal zone lymphoma were stimulated with 5 μg/ml of no ODN (A and D), control ODN (B and E) or CpG ODN (C and F) for 72 hours and analyzed by flow cytometry. A, B, and C illustrate FSC (x-axis) vs. SSC (y-axis). D, E and F illustrate CD19 expression (x-axis) against FSC (y-axis), allowing for separation of B cells from other leukocyte subpopulations. Upon stimulation with CpG ODN, B cells shifted up and to the right, indicating an increase in granularity and size. No changes could be detected without stimulation or on stimulation with the non-CpG ODN.

Expression of CD20, CD40, CD69, CD80, CD86, surface Ig, CD54, MHC I, MHC II, and an HLA-DR variant antigen (moAb 1D10) were examined on viable CD19+ cells after incubation of cells with CpG ODN for 72 hours. Each of these markers was upregulated to varying extents in response to the CpG ODN 2006 compared to the control ODN 2017 (**Fig. 2, Fig. 3**).

Figure 2 depicts the expression of surface antigens on marginal zone lymphoma cells upon CpG ODN treatment. Flow cytometric analysis of surface antigen expression on malignant B cells from a patient with marginal zone lymphoma was performed 72 hours after stimulation with 5 μg/ml of either CpG ODN or non-CpG ODN. On stimulation with CpG ODN, median fluorescence intensity for all markers tested shifted to the right, indicating an increase in surface expression. Thin curves indicate incubation with medium alone, dotted curves incubation with control ODN; and bold curves incubation with CpG ODN.

Figure 3 depicts the expression of surface antigens on primary cells representing different B-cell malignancies and cells of a benign follicular hyperplasia upon CpG ODN treatment. Cells from lymph node biopsies, peripheral blood or pleural fluid from patients with different B-cell malignancies were incubated for 72 hours with either media alone, control ODN or CpG ODN. Each panel represents one experiment.

CD20 was expressed to varying degrees in all samples tested. As is well known, baseline CD20 expression was lower in the B-CLL samples when compared to the B-cell malignancies of other histologies. CpG-ODN 2006 but not the control ODN 2017 increased CD20 expression in both B-CLLs and both marginal zone lymphomas. No or only little upregulation was seen in the other lymphoma samples. Non-malignant CD19+ cells derived from the reactive follicular hyperplasia decreased CD20 expression in response to CpG (**Fig. 3**). This data demonstrated a reverse correlation between the baseline expression of CD20 and CD40, and expression of these markers after incubation with CpG ODN; thus the lower the baseline level of CD20 and CD40, the higher was the responsiveness to CpG ODN (r: -0.6; -0.4) (**Fig. 4**). This correlation was less clear for the other markers. CD19+ cells derived from the reactive follicular hyperplasia showed high baseline expression of activation markers which was not further upregulated by CpG.

Figure 4 shows the CpG ODN effect on CD20 and CD40 is dependent on the baseline level of expression. Cells from lymph node biopsies, peripheral blood or pleural fluid from patients with different B-cell malignancies (see Table 5) were incubated with or

without CpG ODN for 72 hours. Expression of CD20 and CD40 was measured by flow cytometry. Baseline expression of CD20 and CD40 with medium alone was compared to the expression of CD20 and CD40 in the presence of CpG ODN. The coefficients of correlation are indicated.

Table 5: Percentage Of CD19+ Cells In Samples Tested.

Sample Number	Histology	Source	% CD19+ Cells
1	Chronic Lymphocytic Leukemia 1	Peripheral Blood	> 98 %
2	Chronic Lymphocytic Leukemia 2	Peripheral Blood	70 %
3	Large Cell Lymphoma 1	Pleural Fluid	55 %
4	Large Cell Lymphoma 2	Lymph Node	75 %
5	Mantle Cell Lymphoma	Lymph Node	98 %
6	Diffuse Mixed Small and Large Cell Lymphoma	Lymph Node	50 %
7	Marginal Zone Lymphoma 1	Lymph Node	80 %
8	Marginal Zone Lymphoma 2	Peripheral Blood	> 94 %
9	Reactive Follicular Hyperplasia	Lymph Node	35 %

Example 2: Immunostimulatory nucleic acids induce proliferation and apoptosis of malignant B cells.

CpG induces a strong proliferative response of primary human B cells. Hartmann G et al., *J Immunol* 164:944-53 (2000). Two techniques were used to assess whether CpG ODN is capable of inducing proliferation of B-CLL cells. For select samples, cells were stained with CFSE and incubated for four days. Proliferation of cells is indicated by a loss of CFSE stain with every cell division. In B-CLL, CD5 can be used to identify malignant B cells among CD19+ cells. Proliferation of malignant B cells (CD5+ and CD19+) was lower than proliferation of normal B cells (CD5- and CD19+) **(Fig. 5)**. For the marginal zone lymphoma, CpG ODN 2006 induced proliferation of the CD19+ cell population **(Fig. 5)**.

Figure 5 shows a comparison of CpG ODN induced proliferation of malignant and normal B cells. Peripheral blood mononuclear cells from two patients, one with B-CLL and one with marginal zone lymphoma with circulating malignant cells, were incubated for 72 hours with CpG ODN or medium alone and evaluated by two-color flow cytometry. CFSE fluorescence (x-axis) and expression of CD5 (CLL) or CD19 (marginal zone lymphoma) (y-

axis) were evaluated. In CLL, CpG ODN enhanced proliferation of both CD5+ and the CD5- cells. However the relative number of proliferating cells and the number of divisions is lower in the CD5- subset than in the CD5+ subset. In marginal zone lymphoma CpG ODN enhanced proliferation in the CD19+ cell subset.

No consistent pattern was apparent related to determining whether CpG ODN altered the percent of dead cells as determined by morphological criteria (see Table 6).

Table 6: Percent Apoptotic Cells Based On Morphologic Criteria.

Sample Number	Histology	Media	CpG ODN 2006
1	Chronic Lymphocytic Leukemia 1	25.9	21.5
2	Chronic Lymphocytic Leukemia 2	32.6	45.3
3	Large Cell Lymphoma 1	33.9	26.2
4	Large Cell Lymphoma 2	16.0	9.8
5	Mantle Cell Lymphoma	55.1	60.0
6	Diffuse Mixed Small and Large Cell Lymphoma	27.6	26.6
7	Marginal Zone Lymphoma 1	32.9	32.8
8	Marginal Zone Lymphoma 2	38.8	56.0
9	Reactive Follicular Hyperplasia	8.6	18.0

A TUNEL assay was utilized to assess the effect of CpG ODN on both proliferation and apoptosis. The results are shown in Table 7.

Table 7: Apoptosis And Proliferation As Determined By TUNEL.

Sample	Baseline		CpG ODN		Control ODN	
	Apop	Prolif	Apop	Prolif	Apop	Prolif
1663141	15	8	11	10	12	5
12142812	3	<1	1	10	2	12
12141811	<1	<1	<1	11	?	?

Example 3: CpG ODN enhance the therapeutic effect of murine IgG2a (which relates to human IgG1) but not murine IgG1 (which relates to human IgG2) anti-tumor antibody.

CpG ODN when combined with antibody of murine subtype IgG2a dramatically promotes survival in mice having tumors. Mice were injected i.p. with 5000 T3C cells on day 0. They were then given 100 μg anti-idiotype monoclonal antibody as either IgG1 (MS5A10) or IgG2a (MS11G6) on days 5, 7, and 10. In this model, the target antigen is the idiotype expressed by the lymphoma cells. Therefore, the anti-tumor antibodies are also "anti-idiotype." These antibodies (MS5A10 and MS11G6) are simultaneously both anti-tumor antibodies and anti-idiotype antibodies. Twenty micrograms of CpG ODN 1826 (5' TCCATGACGTTCCTGACGTT 3'; SEQ ID NO: 560) was given at the same time. Results are shown in **Figure 6**. Untreated controls had a median survival time (MST) of 17 days after inoculation with tumor. Mice treated with murine IgG1 antibody plus CpG ODN had survival that was similar to those treated with murine IgG1 antibody alone (MST 28 days and 27 days, respectively). In contrast, mice treated with murine IgG2a plus CpG ODN had survival that was significantly improved when compared to mice treated with murine IgG2a alone (MST 45 days and 37 days, respectively).

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

CLAIMS

1. A method for treating or preventing cancer, comprising:

administering to a subject having or at risk of developing cancer an effective amount to upregulate CD20 expression of a nucleic acid, and

an anti-CD20 antibody.

2. The method of claim 1, wherein the nucleic acid is an immunostimulatory CpG nucleic acid having an unmethylated CpG motif.

3. The method of claim 1, wherein the nucleic acid is an immunostimulatory T-rich nucleic acid.

4. The method of claim 1, wherein the nucleic acid is an immunostimulatory poly-G nucleic acid.

5. The method of claim 1, wherein the nucleic acid is bacterial DNA.

6. The method of claim 1, wherein the nucleic acid is eukaryotic DNA.

7. The method of claim 1, wherein the cancer is B-cell lymphoma associated with low levels of CD20 expression.

8. The method of claim 7, wherein the B-cell lymphoma is B-cell chronic lymphocytic leukemia (B-CLL).

9. The method of claim 7, wherein the B-cell lymphoma is a marginal zone lymphoma.

10. The method of claim 1, wherein the anti-CD20 antibody is C2B8.

11. The method of claim 1, wherein the anti-CD20 antibody is Rituximab.

12. The method of claim 1, wherein the nucleic acid does not hybridize with genomic DNA or RNA under stringent conditions.

13. The method of claim 1, wherein the nucleic acid has a modified backbone.

14. The method of claim 13, wherein the modified backbone is a phosphate backbone modification.

15. The method of claim 13, wherein the modified backbone is a peptide modified oligonucleotide backbone.

16. The method of claim 1, wherein the nucleic acid is an immunostimulatory nucleic acid.

17. The method of claim 1, wherein the nucleic acid is 8 to 40 nucleotides in length.

18. The method of claim 1, wherein the nucleic acid is isolated.

19. The method of claim 1, wherein the nucleic acid is a synthetic nucleic acid.

20. The method of claim 1, wherein the nucleic acid and the anti-CD20 antibody are administered together.

21. The method of claim 1, wherein the nucleic acid and the anti-CD20 antibody are administered separately.

22. A method for diagnosing lymphoma, comprising:

isolating a B cell from a subject having or suspected of having a type of lymphoma and identifying a change in a cell surface marker when the B cell is contacted with an immunostimulatory nucleic acid, wherein the cell surface marker induced on the B cell is indicative of the type of lymphoma.

23. The method of claim 22, further comprising a method for treating cancer by administering to the subject an immunostimulatory nucleic acid and an antibody specific for the cell surface marker induced on the B cell in order to treat the cancer.

24. A method for treating or preventing cancer, comprising:

administering to a subject having or at risk of developing cancer an effective amount to induce expression of a surface antigen on a cancer cell surface, of a nucleic acid, and

administering to the subject an antibody selected from the group consisting of an anti-CD22 antibody and an anti-CD19 antibody.

25. The method of claim 24, wherein the nucleic acid is an immunostimulatory CpG nucleic acid having an unmethylated CpG motif.

26. The method of claim 24, wherein the nucleic acid is an immunostimulatory T-rich nucleic acid.

27. The method of claim 24, wherein the nucleic acid is an immunostimulatory poly-G nucleic acid.

28. The method of claim 24, wherein the nucleic acid is bacterial DNA.

29. The method of claim 24, wherein the nucleic acid is eukaryotic DNA.

30. The method of claim 24, wherein the anti-CD22 antibody is a human IgG1 antibody.

31. The method of claim 24, wherein the anti-CD22 antibody is a murine IgG2a antibody.

32. The method of claim 24, wherein the anti-CD19 antibody is a human IgG1 antibody.

33. The method of claim 24, wherein the anti-CD19 antibody is a murine IgG2a antibody.

34. A method for treating lymphoma, comprising:

isolating a B cell from a subject having lymphoma,

identifying a surface antigen which is not expressed or which is expressed on the surface of the B cell in an amount lower than that of a control B cell,

administering to the subject an antibody specific for the identified surface antigen and an immunostimulatory nucleic acid in order to treat the cancer, wherein the immunostimulatory nucleic acid is administered in an effective amount to upregulate expression of the surface antigen on the cancer cell surface.

35. The method of claim 34, wherein the surface antigen is CD20.

36. The method of claim 34, wherein the surface antigen is CD40.

37. The method of claim 34, wherein surface antigen is CD22.

38. The method of claim 34, wherein surface antigen is CD19.

39. The method of claim 34, wherein the lymphoma is B-CLL.

40. The method of claim 34, wherein the lymphoma is marginal zone lymphoma.

41. The method of claim 34, wherein the antibody is a human IgG1 antibody.

42. The method of claim 34, wherein the antibody is a murine IgG2a antibody.

43. A method for treating a lymphoma resistant to antibody therapy, comprising:

administering to a subject having a lymphoma resistant to therapy with an antibody specific for a surface antigen, an antibody specific for the surface antigen to which the lymphoma is resistant and a nucleic acid in order to treat the lymphoma, wherein the nucleic acid is administered in an effective amount to upregulate expression of the surface antigen on the lymphoma cell surface.

44. The method of claim 43, wherein the surface antigen is CD20.

45. The method of claim 44, wherein the antibody is Rituximab.

46. The method of claim 43, wherein the surface antigen is CD40.

47. The method of claim 43, wherein the surface antigen is CD22.

48. The method of claim 43, wherein the surface antigen is CD19.

49. The method of claim 43, wherein the antibody is a human IgG1 antibody.

50. The method of claim 43, wherein the antibody is a murine IgG2a antibody.

51. The method of claim 43, further comprising administering an anti-cancer therapy.

52. The method of claim 51, wherein the anti-cancer therapy is selected from the group consisting of a chemotherapeutic agent or a cancer vaccine.

53. The method of claim 52, wherein the chemotherapeutic agent is selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, valrubicin, Novantrone/Mitroxantrone, Evacet/liposomal doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, Furtulon/Doxifluridine, Cyclopax/oral paclitaxel, SPU-077/Cisplatin, HMR 1275/Flavopiridol, BMS-182751/oral platinum, Leustatin/Cladribine, Paxex/Paclitaxel, Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, Taxotere/Docetaxel, prodrug of guanine arabinoside, nitrosoureas, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Daunorubicin HCl, Etoposide (VP16-213), Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mesna, Mitoxantrone HCl,

Procarbazine HCl, Thioguanine, Thiotepa, Vinblastine sulfate, Azacitidine, Interleukin 2, Pentostatin (2'deoxycoformycin), Teniposide (VM-26), GM-CSF, and Vindesine sulfate.

54. The method of claim 52, wherein the chemotherapeutic agent is selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, valrubicin, Novantrone/Mitroxantrone, Evacet/liposomal doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, SPU-077/Cisplatin, HMR 1275/Flavopiridol, BMS-182751/oral platinum, Leustatin/Cladribine, Paxex/Paclitaxel, Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, Taxotere/Docetaxel, prodrug of guanine arabinoside, nitrosoureas, alkylating agents such as melphalan and cyclophosphamide, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Daunorubicin HCl, Etoposide (VP16-213), Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mitoxantrone HCl, Procarbazine HCl, Thioguanine, Thiotepa, Vinblastine sulfate, Azacitidine, Interleukin 2, Pentostatin (2'deoxycoformycin), Teniposide (VM-26), GM-CSF, and Vindesine sulfate.

55. The method of claim 52, wherein the cancer vaccine is selected from the group consisting of EGF, Anti-idiotypic cancer vaccines, Gp75 antigen, GMK melanoma vaccine, MGV ganglioside conjugate vaccine, Her2/neu, Ovarex, M-Vax, O-Vax, L-Vax, STn-KHL theratope, BLP25 (MUC-1), liposomal idiotypic vaccine, Melacine, peptide antigen vaccines, toxin/antigen vaccines, MVA-based vaccine, PACIS, BCG vaccine, TA-HPV, TA-CIN, DISC-virus and ImmuCyst/TheraCys.

56. A method for treating cancer in a human, comprising:

administering to a human an immunostimulatory nucleic acid and an antibody of IgG1 isotype, which binds to a cell surface antigen of a cancer cell and wherein the nucleic acid and the antibody are administered in an effective amount for killing the cancer cell.

57. The method of claim 56, wherein the nucleic acid is an immunostimulatory CpG nucleic acid having an unmethylated CpG motif.

58. The method of claim 56, wherein the nucleic acid is an immunostimulatory T-rich nucleic acid.

59. The method of claim 56, wherein the nucleic acid is an immunostimulatory poly-G nucleic acid.

60. The method of claim 56, wherein the nucleic acid is bacterial DNA.

61. The method of claim 56, wherein the nucleic acid is eukaryotic DNA.

62. The method of claim 56, wherein the nucleic acid has a modified backbone.

63. The method of claim 62, wherein the modified backbone is a phosphate backbone modification.

64. The method of claim 62, wherein the modified backbone is a peptide modified oligonucleotide backbone.

65. The method of claim 56, wherein the nucleic acid is an immunostimulatory nucleic acid.

66. The method of claim 56, wherein the nucleic acid is 8 to 40 nucleotides in length.

67. The method of claim 56, wherein the nucleic acid is isolated.

68. The method of claim 56, wherein the nucleic acid is a synthetic nucleic acid.

69. The method of claim 56, wherein the nucleic acid and the antibody are administered together.

70. The method of claim 56, wherein the nucleic acid and the antibody are administered separately.

71. The method of claim 56, further comprising administering an anti-cancer therapy.

72. The method of claim 71, wherein the anti-cancer therapy is selected from the group consisting of a chemotherapeutic agent and a cancer vaccine.

73. The method of claim 72, wherein the chemotherapeutic agent is selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, non-sugar containing chloroethylnitrosoureas, 5-fluorouracil, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, fragyline, Meglamine GLA, valrubicin, carmustaine and poliferposan, MMI270, BAY 12-9566, RAS famesyl transferase inhibitor, famesyl transferase inhibitor, MMP, MTA/LY231514, LY264618/Lometexol, Glamolec, CI-994, TNP-470, Hycamtin/Topotecan, PKC412, Valspodar/PSC833, Novantrone/Mitroxantrone, Metaret/Suramin, Batimastat, E7070, BCH-4556, CS-682, 9-AC, AG3340, AG3433, Incel/VX-710, VX-853, ZD0101, ISI641, ODN 698, TA 2516/Marmistat, BB2516/Marmistat, CDP 845, D2163, PD183805, DX8951f, Lemonal DP 2202, FK 317, Picibanil/OK-432, AD 32/Valrubicin, Metastron/strontium derivative, Temodal/Temozolomide, Evacet/liposomal doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, Xeload/Capecitabine, Furtulon/Doxifluridine, Cyclopax/oral paclitaxel, Oral Taxoid, SPU-077/Cisplatin, HMR 1275/Flavopiridol, CP-358 (774)/EGFR, CP-609 (754)/RAS oncogene inhibitor, BMS-182751/oral platinum, UFT(Tegafur/Uracil), Ergamisol/Levamisole, Eniluracil/776C85/5FU enhancer, Campto/Levamisole, Camptosar/Irinotecan, Tumodex/Ralitrexed, Leustatin/Cladribine, Paxex/Paclitaxel, Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, ZD1839, LU 79553/Bis-Naphtalimide, LU 103793/Dolastain, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, ZD 0473/Anormed, YM 116, Iodine seeds, CDK4 and CDK2 inhibitors, PARP inhibitors, D4809/Dexifosamide, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, ZD 9331, Taxotere/Docetaxel, prodrug of guanine arabinoside, Taxane Analog, nitrosoureas, alkylating agents such as melphalan and

cyclophosphamide, Aminoglutethimide, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Dactinomycin, Daunorubicin HCl, Estramustine phosphate sodium, Etoposide (VP16-213), Floxuridine, Fluorouracil (5-FU), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Leuprolide acetate (LHRH-releasing factor analogue), Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mesna, Mitotane (o,p′-DDD), Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Amsacrine (m-AMSA), Azacitidine, Erythropoietin, Hexamethylmelamine (HMM), Interleukin 2, Mitoguazone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG), Pentostatin (2'deoxycoformycin), Semustine (methyl-CCNU), Teniposide (VM-26), GM-CSF, and Vindesine sulfate.

74. The method of claim 72, wherein the chemotherapeutic agent is selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, valrubicin, Novantrone/Mitroxantrone, Evacet/liposomal doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, SPU-077/Cisplatin, HMR 1275/Flavopiridol, BMS-182751/oral platinum, Leustatin/Cladribine, Paxex/Paclitaxel, Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, Taxotere/Docetaxel, prodrug of guanine arabinoside, nitrosoureas, alkylating agents such as melphalan and cyclophosphamide, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Daunorubicin HCl, Etoposide (VP16-213), Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mitoxantrone HCl, Procarbazine HCl, Thioguanine, Thiotepa, Vinblastine sulfate, Azacitidine, Interleukin 2, Pentostatin (2'deoxycoformycin), Teniposide (VM-26), GM-CSF, and Vindesine sulfate.

75. The method of claim 72, wherein the cancer vaccine is selected from the group consisting of EGF, Anti-idiotypic cancer vaccines, Gp75 antigen, GMK melanoma vaccine, MGV ganglioside conjugate vaccine, Her2/neu, Ovarex, M-Vax, O-Vax, L-Vax, STn-KHL

theratope, BLP25 (MUC-1), liposomal idiotypic vaccine, Melacine, peptide antigen vaccines, toxin/antigen vaccines, MVA-based vaccine, PACIS, BCG vaccine, TA-HPV, TA-CIN, DISC-virus and ImmuCyst/TheraCys.

76. A kit, comprising:

a package including at least two containers,

the first container housing an immunostimulatory nucleic acid,

the second container housing an antibody specific for a cell surface antigen, and instructions for screening a cell to determine whether the immunostimulatory nucleic acid upregulates expression of the cell surface antigen.

77. The kit of claim 76, wherein the antibody is selected from the group consisting of an anti-CD20 antibody, an anti-CD19 antibody, and an anti-CD22 antibody.

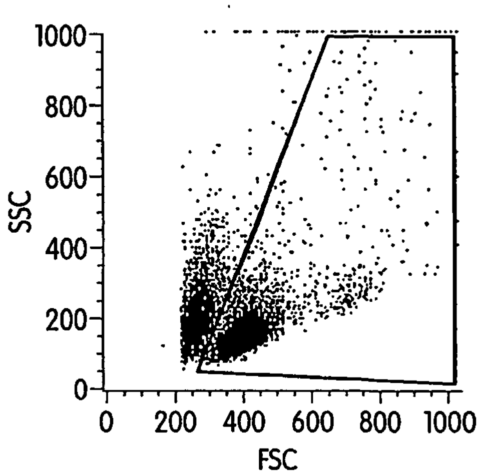


Fig. 1A

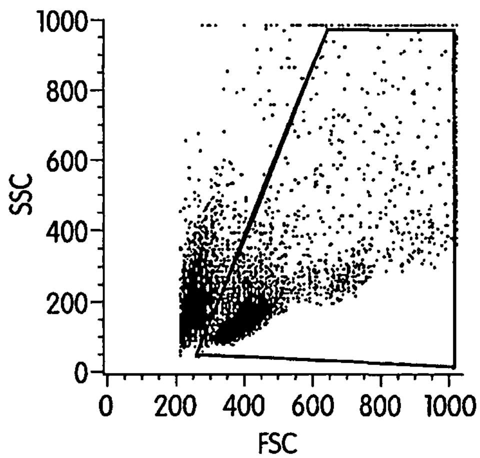


Fig. 1B

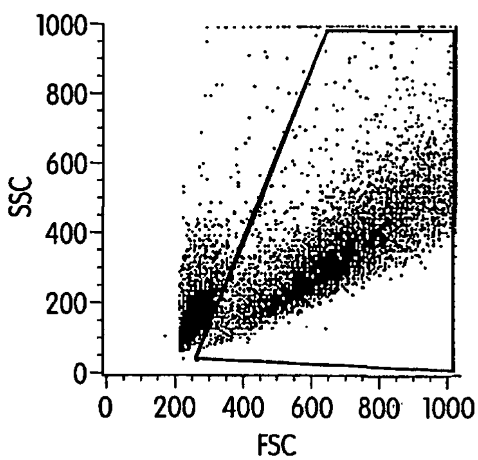


Fig. 1C

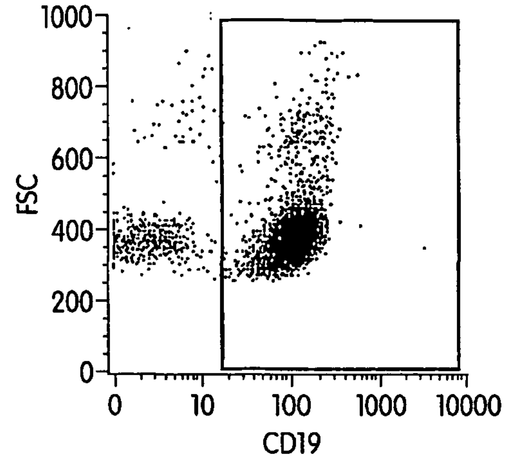


Fig. 1D

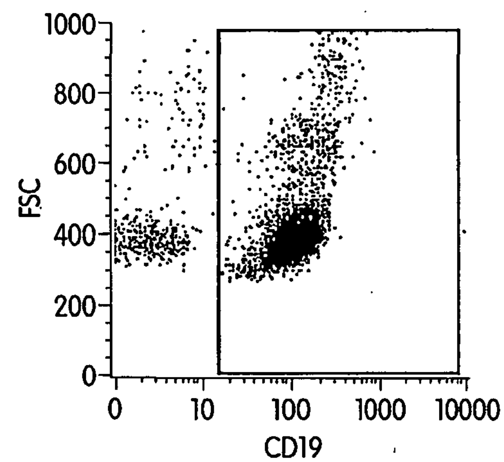


Fig. 1E

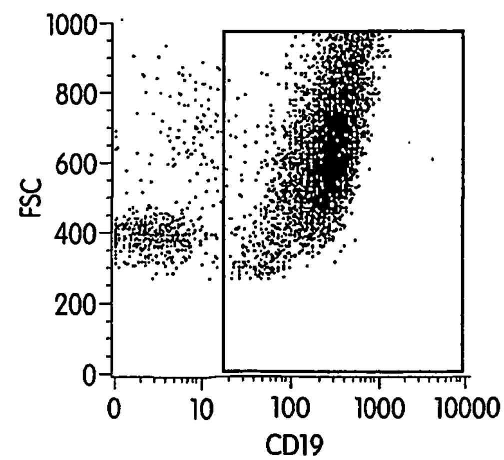
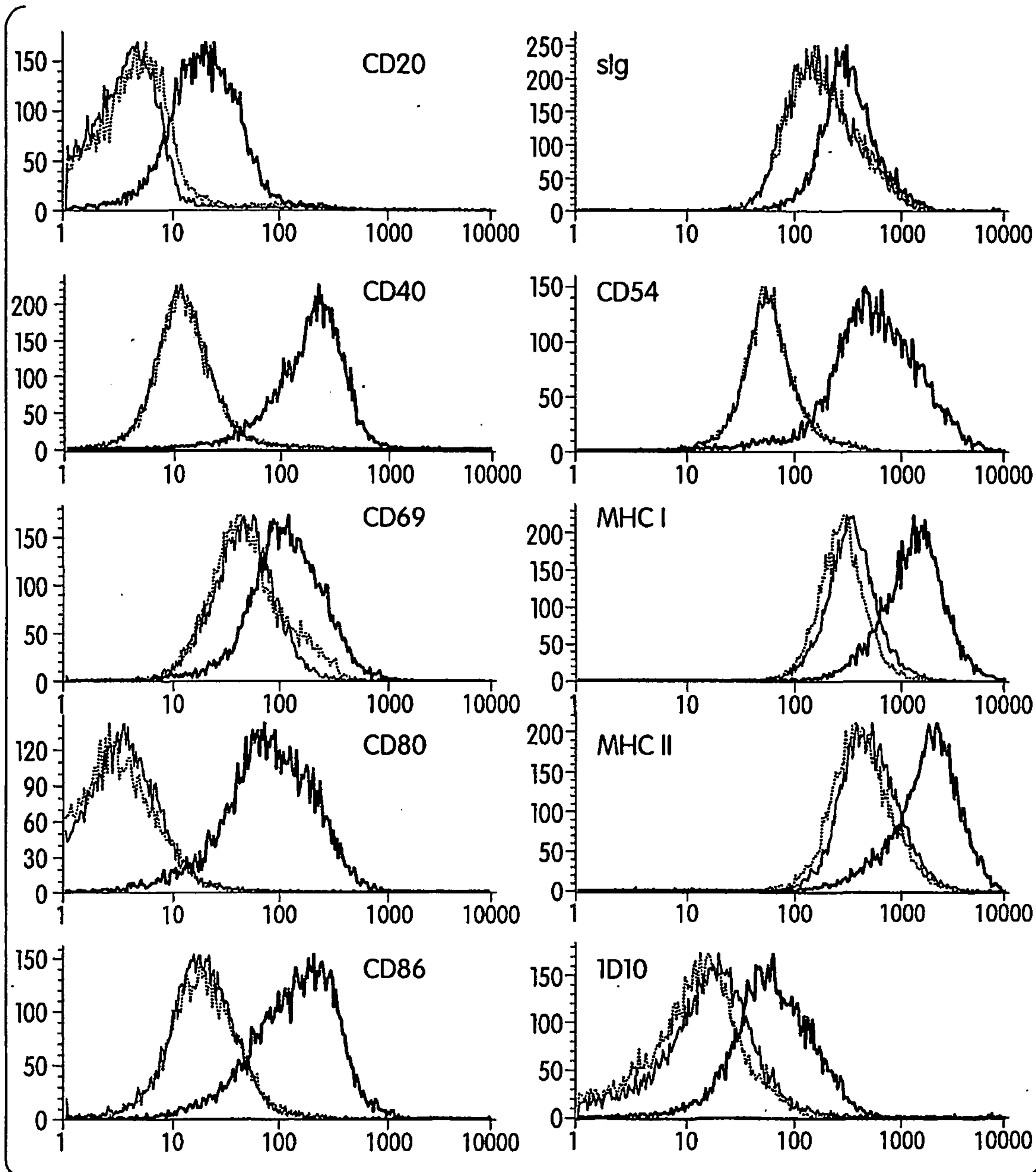


Fig. 1F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CD69
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CD80
MHC II
CD86
1D10
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10
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1000
10000

Fig. 2

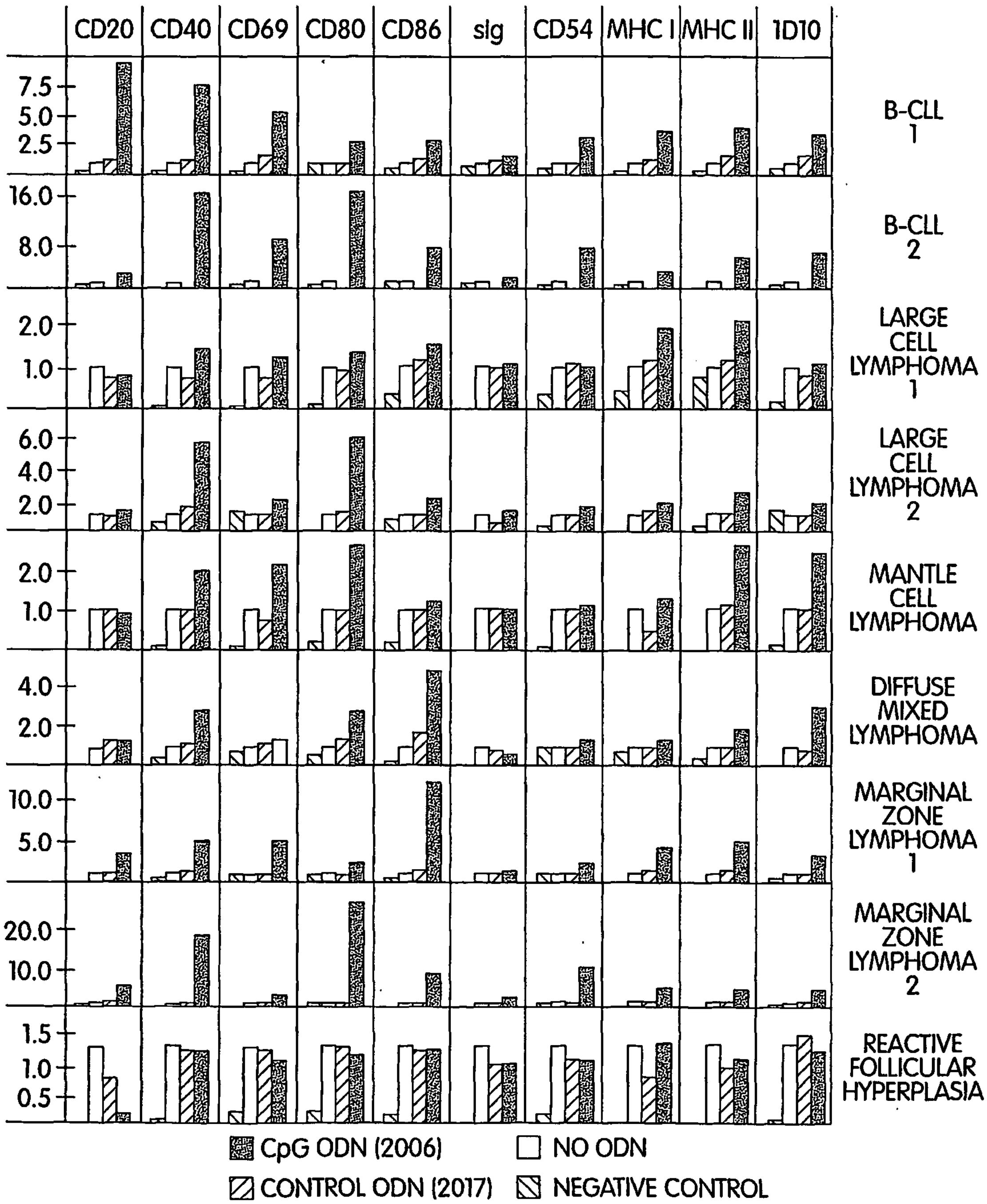

CD20
CD40
CD69
CD80
CD86
sIg
CD54
MHC I
MHC II
1D10
B-CLL 1
B-CLL 2
LARGE CELL LYMPHOMA 1
LARGE CELL LYMPHOMA 2
MANTLE CELL LYMPHOMA
DIFFUSE MIXED LYMPHOMA
MARGINAL ZONE LYMPHOMA 1
MARGINAL ZONE LYMPHOMA 2
REACTIVE FOLLICULAR HYPERPLASIA
7.5
5.0
2.5
16.0
8.0
2.0
1.0
6.0
4.0
2.0
2.0
1.0
4.0
2.0
10.0
5.0
20.0
10.0
1.5
1.0
0.5
CpG ODN (2006)
NO ODN
CONTROL ODN (2017)
NEGATIVE CONTROL

Fig. 3

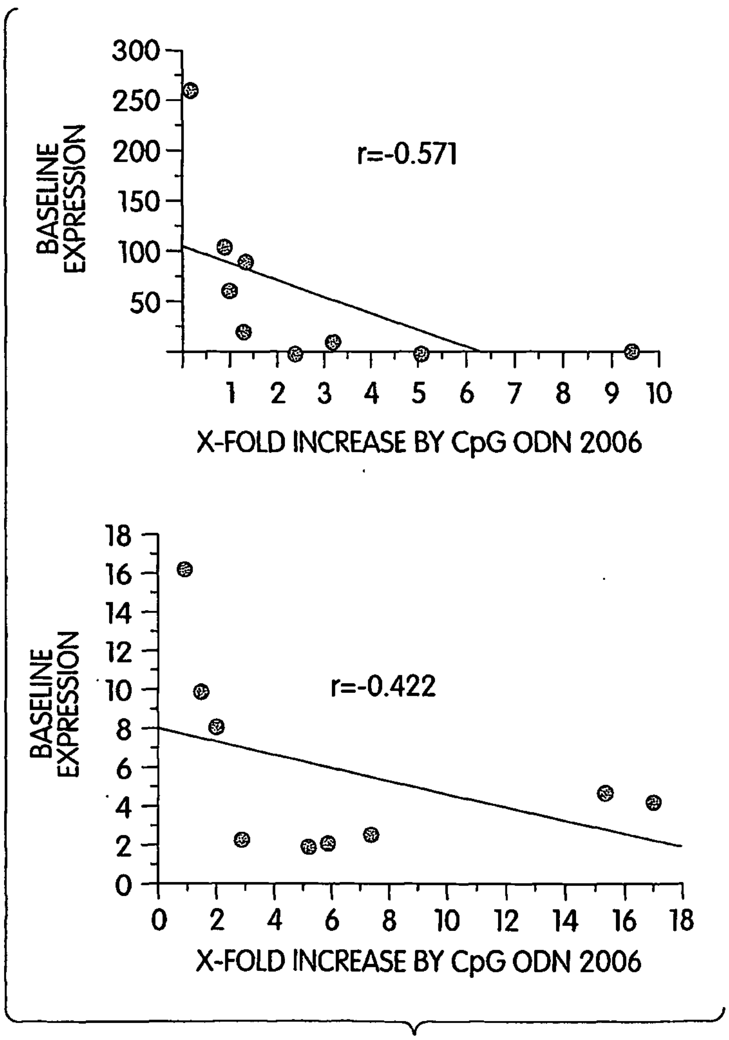
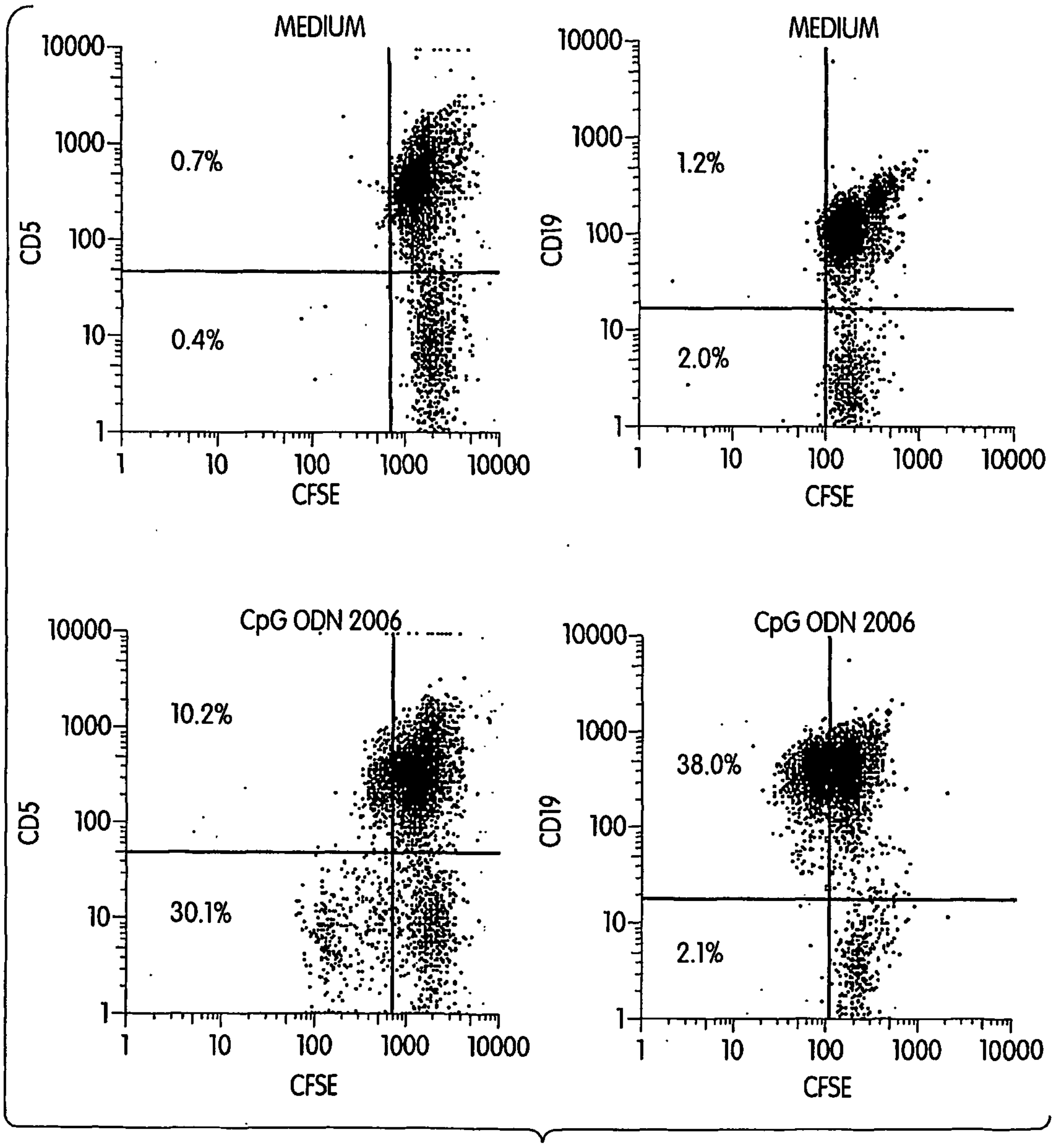

300
250
200
150
100
50
BASELINE EXPRESSION
r=-0.571
1 2 3 4 5 6 7 8 9 10
X-FOLD INCREASE BY CpG ODN 2006
18
16
14
12
10
8
6
4
2
0
BASELINE EXPRESSION
r=-0.422
0 2 4 6 8 10 12 14 16 18
X-FOLD INCREASE BY CpG ODN 2006

Fig. 4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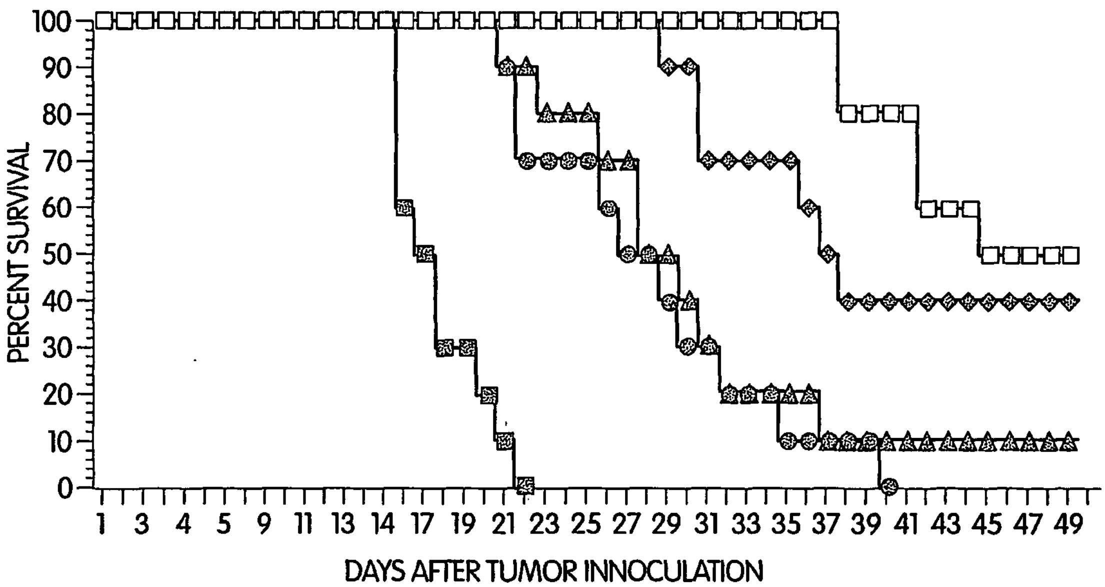
CD5
CFSE
0.7%
0.4%
MEDIUM
CD19
CFSE
1.2%
2.0%
CpG ODN 2006
CD5
CFSE
10.2%
30.1%
CpG ODN 2006
CD19
CFSE
38.0%
2.1%

Fig. 5



100
90
80
70
60
50
40
30
20
10
0
PERCENT SURVIVAL
1 3 4 5 9 11 13 14 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49
DAYS AFTER TUMOR INNOCULATION

Fig. 6

SEQUENCE LISTING

<110> University of Iowa Research Foundation

<120> Methods for Enhancing Antibody-Induced
Cell Lysis and Treating Cancer

<130> C1039/7052WO (AWS)

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<223> phosphorothioate backbone

<400> 35
accatggacg aactgtttcc cctc 24

<210> 36
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 36
accatggacg acctgtttcc cctc 24

<210> 37
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 37
accatggacg agctgtttcc cctc 24

<210> 38
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<400> 38
accatggacg agctgtttcc cctc 24

<210> 39
<211> 24
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<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 39
accatggacg atctgtttcc cctc 24

<210> 40
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 40
accatggacg gtctgtttcc cctc 24

<210> 41
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 41
accatggacg tactgtttcc cctc 24

<210> 42
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 42
accatggacg ttctgtttcc cctc 24

<210> 43
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 43
acccatcaat agctctgtgc 20

<210> 44
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 44
acccgtcgta attatagtaa aaccc 25

<210> 45
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 45
accgcatgga ttctaggcca 20

<210> 46
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 46
accttattaa gattgtgcaa tgtgacgtcc tttagcatcg caaga 45

<210> 47
<211> 16
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<400> 47
acgctggacc ttccat 16

<210> 48
<211> 20

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 48
acgtcgttcc cccccccccc 20

<210> 49
<211> 6
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 49
acgtgt 6

<210> 50
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 50
actagacgtt agtgtga 17

<210> 51
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 51
actagacgtt agtgtga 17

<210> 52

<211> 17
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<220>
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<221> misc_feature
<222> (0)...(0)
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<400> 52
actggacgtt agcgtga 17

<210> 53
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 53
acttctcata gtccctttgg tccag 25

<210> 54
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 54
agaacgtt 8

<210> 55
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<400> 55
agacagacac gaaacgaccg 20

<210> 56
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 56
agactcatgg gaaaatccca catttga 27

<210> 57
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 57
agatagcaaa tcggctgacg 20

<210> 58
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<400> 58
agatggttct cagataaagc ggaa 24

<210> 59
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 59
agcaccgaac gtgagagg 18

<210> 60
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
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<400> 60
agcacggtag ccttccta 18

<210> 61
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 61
agcagcttta gagctttaga gctt 24

<210> 62
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 62
agcatcagga acgacatgga 20

<210> 63
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 63
agcatcagga ccgacatgga 20

<210> 64
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)

<223> phosphodiester backbone

<400> 64
agcgctga 8

<210> 65
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 65
agctcaacgt catgc 15

<210> 66
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 66
agctccatgg tgctcactg 19

<210> 67
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 67
aggatatc 8

<210> 68
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<400> 68

aggtacagcc aggactacga 20

<210> 69
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> modified_base
<222> (3)...(3)
<223> I

<221> modified_base
<222> (8)...(8)
<223> I

<221> modified_base
<222> (14)...(14)
<223> I

<400> 69
agncccgnga acgnattcac 20

<210> 70
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 70
agtgactctc cagcgttctc 20

<210> 71
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 71
agtgcgattc gagatcg 17

<210> 72
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 72
agtgcgattg cagatcg 17

<210> 73
<211> 6
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 73
agtgct 6

<210> 74
<211> 6
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 74
agtgct 6

<210> 75
<211> 10
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 75
agttgcaact 10

<210> 76
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 76
ataaagcgaa actagcagca gtttc 25

<210> 77
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 77
ataacgtt 8

<210> 78
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 78
ataatagagc ttcaagcaag 20

<210> 79
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 79

ataatccagc ttgaaccaag 20

<210> 80
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 80
ataatcgacg ttcaagcaag 20

<210> 81
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 81
ataatcgacg ttcccccccc 20

<210> 82
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 82
ataatcgtcg ttcaagcaag 20

<210> 83
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 83
ataatcgtgc gttcaagaaa g 21

<210> 84
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 84
atagacaaaa attccctccc cggagcc 27

<210> 85
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 85
atatatatat atatatat 18

<210> 86
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 86
atatctaatc aaaacattaa caaa 24

<210> 87
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 87
atcaggaacg tcatgggaag c 21

<210> 88
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 88
atcgacctac gtgcgttctc 20

<210> 89
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> modified_base
<222> (18)...(18)
<223> m5c

<400> 89
atcgacctac gtgcgttntc 20

<210> 90
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 90
atcgactcga gcgttctc 18

<210> 91
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 91
atcgactctc gagcgttctc 20

<210> 92
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> chimeric phosphorothioate/phosphodiester backbone
with phosphorothioate at 5' and 3' ends

<400> 92
atcgactctc gagcgttctc 20

<210> 93
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 93
atcgactctc gagtgttctc 20

<210> 94
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> modified_base
<222> (14)...(14)
<223> m5c

<400> 94
atcgactctc gagngttctc 20

<210> 95
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 95
atcgactctc tcgagcgttc tc 22

<210> 96
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 96
atcgacttcg agcgttctc 19

<210> 97
<211> 17
<212> DNA
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<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
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<400> 97
atcgatcgag cgttctc 17

<210> 98
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 98
atcgatgt 8

<210> 99
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<400> 99
atcggaggac tggcgcgccg 20

<210> 100
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 100
atctggtgag ggcaagctat g 21

<210> 101
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 101
atgacgttcc tgacgtt 17

<210> 102
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 102
atgcactctg cagcgttctc 20

<210> 103
<211> 8

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 103
atgcatgt 8

<210> 104
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 104
atgcccctca acgtt 15

<210> 105
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 105
atgctaaagg acgtcacatt gca 23

<210> 106
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
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<400> 106
atggaaggtc cacgttctc 19

<210> 107

<211> 19
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<220>
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<221> misc_feature
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<400> 107
atggaaggtc cagcgttct 19

<210> 108
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 108
atggaaggtc cagcgttctc 20

<210> 109
<211> 20
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 109
atggaaggtc cagtgttctc 20

<210> 110
<211> 20
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<220>
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<221> misc_feature
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<400> 110
atggaaggtc gagcgttctc 20

<210> 111
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<400> 111
atggactctc cagcgttctc 20

<210> 112
<211> 20
<212> DNA
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 112
atgtcctcgg tcctgatgct 20

<210> 113
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 113
atgtttacta gacaaaattc ccccagaatg ttt 33

<210> 114
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 114
atgtttactt cttaaaattc ccccagaatg ttt 33

<210> 115
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 115
attcgatcgg ggcggggcga g 21

<210> 116
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> modified_base
<222> (3)...(3)
<223> m5c

<400> 116
atngacctac gtgcgttctc 20

<210> 117
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> modified_base
<222> (3)...(3)
<223> m5c

<221> modified_base
<222> (10)...(10)
<223> m5c

<221> modified_base
<222> (14)...(14)
<223> m5c

<400> 117
atngactctn gagngttctc 20

<210> 118
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> misc_feature
<222> (1)...(1)
<223> biotinylated at 5' end

<400> 118
atggaaggtc cagcgttctc 20

<210> 119
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> misc_feature
<222> (1)...(1)
<223> biotinylated 5' end

<400> 119
gagaacgctc cagcactgat 20

<210> 120
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> misc_feature
<222> (1)...(1)
<223> biotinylated 5' end

<400> 120
gagaacgctc gaccttcgat 20

<210> 121
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> misc_feature
<222> (1)...(1)
<223> biotinylated 5' end

<221> modified_base
<222> (6)...(6)
<223> m5c

<400> 121
gagaangctc cagcactgat 20

<210> 122
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> misc_feature
<222> (1)...(1)
<223> biotinylated 5' end

<221> modified_base
<222> (6)...(6)
<223> m5c

<400> 122
gagaangctc gaccttcgat 20

<210> 123
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> misc_feature
<222> (1)...(1)
<223> biotinylated at 5' end

<400> 123
gagcaagctg gaccttccat 20

<210> 124
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> misc_feature
<222> (1)...(1)
<223> biotinylated at 5' end

<221> modified_base
<222> (8)...(8)
<223> m5c

<400> 124
gagcaagntg gaccttccat 20

<210> 125
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
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<223> biotinylated at 5' end

<400> 126
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<400> 127
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<210> 128
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<400> 128
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with phosphodiester on 5' end

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<400> 129
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<400> 131
tcgtcgtttt gtcgttttgt cgttttttt 29

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with phosphodiester on 5' end

<221> misc_feature
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<400> 132
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with phosphodiester on 5' end

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<400> 133
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<400> 134
caaacgtt 8

<210> 135
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<400> 135
caacgtt 7

<210> 136
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caagagatgc taacaatgca 20

<210> 137
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<400> 137
caatcaatct gaggagaccc 20

<210> 138
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<220>
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cacaccttgg tcaatgtcac gt 22

<210> 139
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<400> 139
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<210> 140
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<213> Artificial Sequence

<220>
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<400> 140
cacggtagcc ttccta 16

<210> 141
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<400> 141
cacgttgagg ggcat 15

<210> 142
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<221> misc_feature
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with phosphorothioate at 5' and 3' ends

<400> 142
cactgtcctt cgtcga 16

<210> 143
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<400> 143
cagacacaga agcccgatag acg 23

<210> 144
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<220>
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<221> misc_feature

<222> (0)...(0)
<223> phosphodiester backbone

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cagattgtgc aatgtctcga 20

<210> 145
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<212> DNA
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<220>
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<221> misc_feature
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<210> 146
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<212> DNA
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<220>
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<222> (0)...(0)
<223> phosphodiester backbone

<400> 146
cataggatct cgagctcgga aagtccccta c 31

<210> 147
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<220>
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<221> misc_feature
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<400> 147
catgagctca tctggaggaa gcgg 24

<210> 148
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<220>
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<221> misc_feature
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<223> phosphodiester backbone

<400> 148
catttccacg atttccca 18

<210> 149
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<400> 149
cattttacgg gcgggcgggc 20

<210> 150
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<220>
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<400> 150
ccaaatatcg gtggtcaagc ac 22

<210> 151
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<221> misc_feature
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<400> 151
ccaacgtt 8

<210> 152
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<221> misc_feature
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<400> 152
ccacgtcgac cctcaggcga 20

<210> 153
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<220>
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<221> misc_feature
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<223> phosphodiester backbone

<400> 153
ccacgtggac ctctagc 17

<210> 154
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<221> misc_feature
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<400> 154
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<210> 155
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<400> 155
ccagatgagc tcatgggttt ctcc 24

<210> 156
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<220>
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<400> 156
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<400> 157
ccaggttgta tagaggc 17

<210> 158
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<400> 158
ccagtgctga tcaccgatat cctgttcggc agtcg 35

<210> 159
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<222> (0)...(0)
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<400> 159
ccatcgat 8

<210> 160
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<400> 160
ccatgcat 8

<210> 161
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<400> 161
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<221> misc_feature
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<400> 162
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<210> 163
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<400> 163
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<210> 164
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 164
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<210> 165
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 165
cccccc 6

<210> 166
<211> 8
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 166
cccccccc 8

<210> 167
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<213> Artificial Sequence

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<222> (0)...(0)
<223> phosphorothioate backbone

<400> 167
cccccccccc cc 12

<210> 168
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<400> 168
cccccccccc cccccccccc 20

<210> 169
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with phosphorothioate at 5' and 3' ends

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<210> 170
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<400> 170
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<210> 171
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<400> 171
cccccccccc cccccccccc cccccccc 28

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with phosphorothioate at 5' and 3' ends

<400> 173
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<210> 175
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<400> 175
ccgaacagga tatcggtgat cagcac 26

<210> 176
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<400> 176
ccgcttcctc cagatgagct catg 24

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<221> misc_feature
<222> (0)...(0)
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<400> 177
ccgcttcctc cagatgagct catgggtttc tccaccaag 39

<210> 178
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<400> 178
ccggccggcc ggccggccgg 20

<210> 179
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<221> misc_difference
<222> (0)...(0)
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<400> 179
ccgtcgttcc cccccccccc 20

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<400> 180
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<210> 181
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<400> 181
cctccaaatg aaagaccccc 20

<210> 182
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<220>
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<400> 182
cctctataca acctgggac 19

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with phosphorothioate at 5' and 3' ends

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<210> 184
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<221> misc_difference
<222> (0)...(0)
<223> phosphodiester backbone

<400> 184
ccttcgat 8

<210> 185
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<222> (0)...(0)
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<400> 185
cgaacgtt 8

<210> 186
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 186
cgacga 6

<210> 187
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 187
cgacgt 6

<210> 188
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 188
cgactctcga gcgttctc 18

<210> 189
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<212> DNA
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<220>
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<400> 189
cgactgccga acaggatatc ggtgatcagc actgg 35

<210> 190
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<221> misc_feature
<222> (0)...(0)
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<400> 190
cgccgtcgcg gcggttgg 18

<210> 191
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<221> misc_feature
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<400> 191
cgcctggggc tggtctgg 18

<210> 192
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<221> misc_feature
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cgcgcgcgcg cgcgcgcgcg 20

<210> 193
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<220>
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<400> 193
cgcgcgcgcg cgcgcgcgcg 20

<210> 194
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<221> misc_feature
<222> (0)...(0)
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<400> 194
cgcgta 6

<210> 195
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<221> misc_feature
<222> (0)...(0)
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<400> 195
cgctagaggt tagcgtga 18

<210> 196
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 196
cgctggacct tccat 15

<210> 197
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<220>
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<221> misc_feature
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<223> chimeric phosphorothioate/phosphodiester backbone
with phosphorothioate at 5' and 3' ends

<400> 197
cgctggacct tccatgtcgg 20

<210> 198
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 198
cggctgacgt catcaa 16

<210> 199
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<220>
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<400> 199
cgggcgactc agtctatcgg 20

<210> 200
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<212> DNA
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<220>
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<400> 200
cgggcttacg gcggatgctg 20

<210> 201
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<220>
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<400> 201
cggtagcctt ccta 14

<210> 202
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<400> 202
cgtaccttac ggtga 15

<210> 203
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 203
cgtacg 6

<210> 204
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 204
cgtcga 6

<210> 205
<211> 6
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 205
cgtcga 6

<210> 206
<211> 6
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 206
cgtcgt 6

<210> 207
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 207
cgtcgtcgt 9

<210> 208
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<220>
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<221> misc_feature
<222> (0)...(0)
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<400> 208
cgtcgtcgtc gtcgtcgtcg t 21

<210> 209
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<212> DNA
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<220>
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<400> 209
cgtctatcgg gcttctgtgt ctg 23

<210> 210
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<221> misc_feature
<222> (0)...(0)
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<400> 210
cgttcg 6

<210> 211
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<213> Artificial Sequence

<220>
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<221> misc_feature
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<400> 211
ctaacgtt 8

<210> 212
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<221> misc_feature
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<400> 212
ctaatctttc taattttttt ctaa 24

<210> 213
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 213
ctagataaag cggaaccagc aacagacaca gaagccccga tagag 45

<210> 214
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<212> DNA
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<220>

<223> Synthetic oligonucleotide

<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 214
ctagcgct 8

<210> 215
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 215
ctagcggctg acgtcataaa gctagc 26

<210> 216
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 216
ctagcggctg acgtcatcaa gctag 25

<210> 217
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<221> misc_feature
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<400> 217
ctagcggctg acgtcatcaa tctag 25

<210> 218
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<400> 218
ctagcggctg agctcataaa gctagc 26

<210> 219
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<221> misc_feature
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ctaggctgac gtcatcaagc tagt 24

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<221> misc_feature
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ctagtggctg acgtcatcaa gctag 25

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<400> 224
ctatcggagg actggcgcgc c 21

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<400> 225
ctatcggagg actggcgcgc cg 22

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<221> misc_feature
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ctccagctcc aagaaaggac g 21

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ctcgccccgc cccgatcgaa t 21

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<400> 230
ctctccaagc tcacttacag 20

<210> 231
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<223> phosphorothioate backbone

<400> 231
ctctctgtag gcccgcttgg 20

<210> 232
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<400> 232
ctcttgcgac ctggaaggta 20

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<400> 233
ctgacgtcat 10

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<400> 234
ctgacgtg 8

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<211> 18

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<221> misc_feature
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<400> 235
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ctgattgctc tctcgtga 18

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<400> 237
ctgcagcctg ggac 14

<210> 238
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<221> misc_feature
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<223> phosphodiester backbone

<400> 238
ctgcgttagc aatttaactg tg 22

<210> 239
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<221> misc_feature
<222> (0)...(0)
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<400> 239
ctgctgagac tggag 15

<210> 240
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<221> misc_feature
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<400> 240
ctgctgctgc tgctgctgct g 21

<210> 241
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<221> misc_feature
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with phosphorothioate at 5' and 3' ends

<400> 241
ctggaccttc catgtc 16

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with phosphorothioate at 5' and 3' ends

<400> 242
ctggaccttc catgtcgg 18

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<221> misc_feature
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ctggtctttc tggtttttt ctgg 24

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<223> phosphodiester backbone

<400> 244
ctggtctttc tggtttttt ctgg 24

<210> 245
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<220>
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<400> 245
ctgtaagtga gcttggagag 20

<210> 246
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<220>
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<221> misc_feature
<222> (0)...(0)
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<400> 246
ctgtatgaaa caaattttcc tctttgggca 30

<210> 247
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<222> (0)...(0)
<223> phosphorothioate backbone

<400> 247
ctgtca 6

<210> 248
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<221> misc_feature
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<223> phosphodiester backbone

<400> 248
ctgtcaggaa ctgcaggtaa gg 22

<210> 249
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<400> 249
ctgtcccata tttttagaca 20

<210> 250
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<221> misc_feature
<222> (0)...(0)
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<400> 250
ctgtcg 6

<210> 251
<211> 6
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<400> 251
ctgtcg 6

<210> 252
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<400> 252
ctgtcgttcc cccccccccc 20

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<221> misc_feature
<222> (0)...(0)
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<400> 253
ctgtgctttc tgtgtttttc tgtg 24

<210> 254
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<220>
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<400> 254
cttggagggc ctcccggcgg 20

<210> 255
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<220>

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<221> misc_feature
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<223> phosphodiester backbone

<400> 255
cttggtggag aaacccatga g 21

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<400> 256
cttggtggag aaacccatga gctcatctgg aggaagcgg 39

<210> 257
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<223> phosphorothioate backbone

<400> 257
ctttccgttg gacccctggg 20

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<221> misc_feature
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<223> m5c

<221> modified_base
<222> (6)...(6)
<223> m5c

<221> modified_base
<222> (10)...(10)
<223> m5c

<221> modified_base
<222> (15)...(15)
<223> m5c

<400> 258
cnggcnggcn gggcnccgg 19

<210> 259
<211> 8
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<221> misc_feature
<222> (0)...(0)
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<221> misc_feature
<222> (1)...(1)
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<400> 259
aacgttga 8

<210> 260
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<221> misc_feature
<222> (0)...(0)
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<221> misc_feature
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cgcgaattcg cg 12

<210> 261
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tcaacgtt 8

<210> 262
<211> 8
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<222> (0)...(0)
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<400> 262
gaaacgtt 8

<210> 263
<211> 25
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<221> misc_feature
<222> (0)...(0)
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<400> 263
gaaactgctg ctagtttcgc tttat 25

<210> 264
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<400> 264
gaaccttcca tgctgtt 17

<210> 265
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<400> 265

gaaccttcca tgctgttccg 20

<210> 266
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<400> 266
gaacgctgga ccttccat 18

<210> 267
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gaagttcacg ttgaggggca t 21

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<400> 268
gaagtttctg gtaagtcttc g 21

<210> 269
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<400> 269
gaccttccat 10

<210> 270
<211> 22
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<220>
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<400> 270
gaccttccat gtcggtcctg at 22

<210> 271
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<212> DNA
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<220>
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<400> 271
gaccttctat gtcggtcctg 20

<210> 272
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<400> 272
gacgtcat 8

<210> 273
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<400> 273
gactgacgtc agcgt 15

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gagaacgatg gaccttccat 20

<210> 275
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<400> 275
gagaacgcta gaccttctat 20

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<400> 276
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gagaacgctc cgaccttcga t 21

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<221> misc_feature
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<223> biotinylated at 3' end

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<223> phosphodiester backbone

<400> 282
gagaacgctg gacctatcca t 21

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gagaacgctg gacctcatca tccat 25

<210> 284
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<400> 284
gagaacgctg gacctcatcc at 22

<210> 285
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<400> 285
gagaacgctg gaccttcc 18

<210> 286
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<220>
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<400> 286

gagaacgctg gaccttccat 20

<210> 287
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<221> misc_feature
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<223> phosphorothioate backbone

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gagaacgctg gaccttccat 20

<210> 288
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<400> 288
gagaacgctg gaccttccat gt 22

<210> 289
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<400> 289
gagaacgctg gaccttcgat 20

<210> 290
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<210> 291

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gagaacgctg gaccttgcat 20

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<221> misc_feature
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<400> 292
gagaacgctg gacgctcatc cat 23

<210> 293
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gagaacgctg gacttccat 19

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<221> misc_feature
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<400> 295
gagaacgctg gatccat 17

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<221> modified_base
<222> (6)...(6)
<223> m5c

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<223> Synthetic oligonucleotide

<400> 298
gagaccgctc gaccttcgat 20

<210> 299
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<220>
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<221> misc_feature
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<223> phosphorothioate backbone

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<210> 300
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<221> misc_feature
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<221> misc_feature
<222> (20)...(20)
<223> biotinylated at 3' end

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<210> 301
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

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gaggaacgtc atggagagga acgtcatgga gaggaacgtc atgga 45

<210> 302
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<221> modified_base
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<223> I

<221> modified_base
<222> (11)...(11)
<223> I

<221> modified_base
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<223> I

<400> 302
gaggaaggng nggangacgt 20

<210> 303
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<400> 303
gaggggacca ttttacgggc 20

<210> 304
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<220>
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<221> misc_feature
<222> (0)...(0)
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<400> 304
gatccagatt ctgccaggtc actgtgactg gat 33

<210> 305
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<220>
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<221> misc_feature
<222> (0)...(0)
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<400> 305
gatccagatt ctgctgagtc actgtgactg gat 33

<210> 306
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<221> misc_feature
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<400> 306
gatccagtca cagtgacctg gcagaatctg gat 33

<210> 307
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<221> misc_feature
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<400> 307
gatccagtca cagtgactca gcagaatctg gat 33

<210> 308
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<221> misc_feature
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<223> phosphodiester backbone

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gatccggctg actcatcact agatc 25

<210> 309
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<221> misc_feature
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<223> chimeric phosphorothioate/phosphodiester backbone
with phosphorothioate at 5' and 3' ends

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gatcgctgat ctaatgctcg 20

<210> 310
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<220>
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<400> 310
gatcggagga ctggcgcgcc g 21

<210> 311
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<400> 311
gatctagtga tgagtcagcc ggatc 25

<210> 312
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<221> misc_feature
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<400> 312
gattcaactt gcgctcatct taggc 25

<210> 313
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<400> 317
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<221> misc_feature
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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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<223> m5c

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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<400> 332
gccaccaaaa cttgtccatg 20

<210> 333
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<210> 337

<211> 20
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<220>
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<400> 337
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<400> 341
gcgccagtcc tccgatagac 20

<210> 342
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<223> phosphodiester backbone

<400> 342
gcgcgcgcgc gcgcgcgcg 19

<210> 343
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<220>
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<400> 343
gcgctaccgg tagcctgagt 20

<210> 344
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<210> 345
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gcgtttttttt ttgcg 15

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gctaccttag ngtga 15

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gctacttagc gtga 14

<210> 357
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<222> (0)...(0)
<223> phosphodiester backbone

<400> 357
gctagacgat agcgt 15

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<400> 358
gctagacgct agcgtga 17

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<400> 359
gctagacgt 9

<210> 360
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gctagacgta agcgtga 17

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gctagacgtt agcgt 15

<210> 364
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<400> 364
gctagacgtt agcgtga 17

<210> 365
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with phosphorothioate at 5' and 3' ends

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gctagacgtt agctgga 17

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gctagacgtt aggctga 17

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gctagacgtt agngt 15

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<210> 376
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<210> 377
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<400> 377
gctagatgtt agcgtga 17

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<400> 380
gctagcttta gagctttaga gctt 24

<210> 381
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<400> 381
gctaggcgtt agcgt 15

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<400> 382
gctagtcgat agc 13

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gctagtcgat agcgt 15

<210> 384
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gctandcghh agc 13

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gctatgacgt tccaaggg 18

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gctcga 6

<210> 388
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with phosphorothioate at 5' and 3' ends

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gctcgttcag cgcgtct 17

<210> 389
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<400> 389
gctgaacctt ccatgctgtt 20

<210> 390
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with phosphorothioate at 5' and 3' ends

<400> 390
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<210> 391
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<220>
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<400> 391
gctggacctt ccat 14

<210> 392
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<213> Artificial Sequence

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gctggacctt ccat 14

<210> 393
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<400> 393
gctggccagc ttacctcccg 20

<210> 394
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with phosphorothioate at 5' and 3' ends

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<210> 395
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<210> 396
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<210> 397
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gcttgacgtc tagc 14

<210> 398
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with phosphorothioate at 5' and 3' ends

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<400> 400
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<210> 401
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<400> 401
ggaacgtt 8

<210> 402
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<221> misc_feature
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<223> phosphodiester backbone

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ggaagacgtt aga 13

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<221> misc_feature
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<223> phosphodiester backbone

<400> 403
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<210> 404
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<221> misc_feature
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<400> 404
ggagaaaccc atgagctcat ctgg 24

<210> 405
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<400> 405
ggagctcttc gaacgccata 20

<210> 406
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<400> 406
ggcagtgcag gctcaccggg 20

<210> 407
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<400> 407
ggccaacttt caatgtggga tggcctc 27

<210> 408
<211> 21
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ggctatgtcg ttcctagcc 19

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<400> 416
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with phosphorothioate at 5' and 3' ends

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<210> 418
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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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<400> 427
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<210> 428
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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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<400> 451
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ggtgaggtg 9

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<400> 458
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<400> 460
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gtcccaggtt gtatagaggc tgc 23

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<400> 462
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with phosphorothioate at 5' and 3' ends

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<400> 465
gtctatcgga ggactggcgc 20

<210> 466
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<400> 466
gtctgtccca tgatctcgaa 20

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<400> 471
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<210> 472
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<400> 472
gtgcttgacc accgatattt gg 22

<210> 473
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<400> 473
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<400> 474
gtgtcggggt ctccgggc 18

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<400> 475
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<210> 476
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<400> 476
gttgaaaccc gagaacatca t 21

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<400> 477
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taaacgtt 8

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taagcgct 8

<210> 483
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<400> 483
taagctctgt caacgccagg 20

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<210> 485
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with phosphorothioate at 5' and 3' ends

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<400> 490
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<400> 491
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with phosphorothioate at 5' and 3' ends

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tatgccgcgc ccggacttat 20

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tcaacgt 7

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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<210> 591
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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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<210> 602
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with phosphorothioate at 5' and 3' ends

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<210> 609
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with phosphorothioate at 5' and 3' ends

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<210> 611

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<210> 617
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with phosphorothioate at 5' and 3' ends

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<400> 626
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<400> 678
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<210> 679
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<221> misc_feature
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<400> 679
tcctgtcgtt ccttgtcgtt 20

<210> 680
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<221> misc_feature
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<400> 680
tcctgtcgtt gaagt 15

<210> 681
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<221> misc_feature
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<400> 681
tcctgtcgtt gaagtttttt 20

<210> 682
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<221> misc_feature
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<210> 683
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tccttacgtt gaagt 15

<210> 684
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<221> misc_feature
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<400> 684
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<210> 685
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tcgacgtc 8

<210> 686
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<400> 686
tcgacgttcc cccccccccc 20

<210> 687
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<400> 687
tcgagacatt gcacaatcat ctg 23

<210> 688

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<400> 688
tcgccgttcc cccccccccc 20

<210> 689
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<221> misc_feature
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<400> 689
tcgcgtgcgt tttgtcgttt tgacgtt 27

<210> 690
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<220>
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<222> (0)...(0)
<223> phosphodiester backbone

<400> 690
tcgga 5

<210> 691
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<400> 691
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<210> 692
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<400> 692
tcgtag 6

<210> 693
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tcgtca 6

<210> 694
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<210> 695
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<222> (0)...(0)
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tcgtcgatcc cccccccccc 20

<210> 696
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<400> 696
tcgtcgctcc cccccccccc 20

<210> 697
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<221> misc_feature
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<400> 697
tcgtcgctgt ctccg 15

<210> 698
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<221> misc_feature
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<400> 698
tcgtcgctgt ctccgcttct t 21

<210> 699
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<221> misc_feature
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with phosphodiester on 3' end

<400> 699
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<210> 700
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<221> misc_feature
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<400> 700
tcgtcgctgt ctccgcttct t 21

<210> 701
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<400> 701
tcgtcgctgt ctccgcttct tcttgcc 27

<210> 702
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<220>
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<221> misc_feature
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<400> 702
tcgtcgctgt ctgcccttct t 21

<210> 703
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<221> misc_feature
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<223> phosphorothioate backbone

<400> 703
tcgtcgctgt tgtcgtttct t 21

<210> 704
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<400> 704
tcgtcggtcc cccccccccc 20

<210> 705
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<221> misc_feature
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<400> 705
tcgtcgtcag ttcgctgtcg 20

<210> 706
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<221> misc_feature
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<400> 706
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<210> 707
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<400> 707
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<210> 708
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<400> 708
tcgtcgtcgt cgtt 14

<210> 709
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<221> misc_feature
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<223> chimeric phosphorodithioate/phosphodiester backbone with phosphodiester on 3' end

<400> 709
tcgtcgtcgt cgtt 14

<210> 710
<211> 14
<212> DNA
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<220>
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<221> misc_feature
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<400> 710
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<210> 711
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<400> 711
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<400> 712
tcgtcgttcc cccccccccc 20

<210> 713
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<221> misc_feature
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<223> biotinylated at 3' end

<400> 713
tcgtcgttcc cccccccccc 20

<210> 714
<211> 20
<212> DNA
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<221> misc_feature
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<221> modified_base
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<223> m5c

<400> 714
tcgtcgttcc cccccncccc 20

<210> 715
<211> 26
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 715
tcgtcgttgg tgtcgttggt gtcgtt 26

<210> 716
<211> 24
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<220>
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 716
tcgtcgttgg ttgtcgtttt ggtt 24

<210> 717
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<221> misc_feature
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<223> phosphorothioate backbone

<400> 717
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<210> 718
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<221> misc_feature

<222> (0)...(0)
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<400> 718
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<210> 719
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<221> misc_feature
<222> (0)...(0)
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<400> 719
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<210> 720
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<400> 720
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<210> 721
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<221> misc_feature
<222> (0)...(0)
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<400> 721
tcgtcgtttc gtcgttttga cgtt 24

<210> 722
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<221> misc_feature
<222> (0)...(0)
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<400> 722
tcgtcgtttg cgtgcgtttc gtcgtt 26

<210> 723
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<400> 723
tcgtcgtttg tcgttttgtc gtt 23

<210> 724
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<400> 724
tcgtcgtttt gacgttttga cgtt 24

<210> 725
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<400> 725
tcgtcgtttt gacgttttgt cgtt 24

<210> 726
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<400> 726
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<210> 727
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<220>
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<400> 727
tcgtcgtttt gtcgttttgg gggg 24

<210> 728
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<400> 728
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<210> 729
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<221> misc_feature
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<400> 729
tcgtcgtttt gtcgttttgt cgtt 24

<210> 730
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with phosphorothioate at 5' and 3' ends

<400> 730
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<210> 731
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<222> (0)...(0)
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<400> 731
tcgtcgtttt gtcgttttgt cgtt 24

<210> 732
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<222> (0)...(0)
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<400> 732
tcgtcgtttt gtcgttttgt cgtt 24

<210> 733
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<222> (0)...(0)
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<221> misc_feature
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<223> biotinylated at 3' end

<400> 733
tcgtcgtttt gtcgttttgt cgtt 24

<210> 734
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<221> misc_feature
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<400> 734
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<210> 735
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<221> misc_feature
<222> (0)...(0)
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<400> 735
tcgtcgtttt gtggttttgt ggtt 24

<210> 736
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<221> misc_feature
<222> (0)...(0)
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<400> 736
tcgtcgtttt ttgtcgtttt ttgtcgtt 28

<210> 737
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 737
tcgtcgtttt tttttttttt 20

<210> 738

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<221> misc_feature
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<400> 738
tcgtga 6

<210> 739
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<221> misc_feature
<222> (0)...(0)
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<400> 739
tcgtga 6

<210> 740
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 740
tcgtgg 6

<210> 741
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<221> misc_feature
<222> (0)...(0)
<223> phosphodiester backbone

<221> modified_base
<222> (5)...(5)
<223> m5c

<400> 741
tcgtngttcc cccccccccc 20

<210> 742
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<221> misc_feature
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<400> 742
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<210> 743
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<221> misc_feature
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<223> phosphodiester backbone

<400> 743
tctaaaaacc atctattctt aacccct 26

<210> 744
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<221> misc_feature
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with phosphorothioate at 5' and 3' ends

<400> 744
tctagcgttt ttagcgttcc 20

<210> 745
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<221> misc_feature

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<400> 745
tctatcccag gtggttcctg ttag 24

<210> 746
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<210> 747
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<221> misc_feature
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<400> 747
tctccatcct atggttttat cg 22

<210> 748
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<400> 748
tctccatgat ggttttatcg 20

<210> 749
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<400> 749
tctcccagcg agcgagcgcc at 22

<210> 750
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<221> misc_feature
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<400> 750
tctcccagcg agcgccat 18

<210> 751
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 751
tctcccagcg cgcgccat 18

<210> 752
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 752
tctcccagcg ggcgcat 17

<210> 753
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 753
tctcccagcg tacgccat 18

<210> 754
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<221> misc_feature
<222> (0)...(0)
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<400> 754
tctcccagcg tcgccat 17

<210> 755
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<221> misc_feature
<222> (0)...(0)
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<400> 755
tctcccagcg tgcgccat 18

<210> 756
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<223> phosphodiester backbone

<400> 756
tctcccagcg tgcgccat 18

<210> 757
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<221> misc_feature
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<223> chimeric phosphorothioate/phosphodiester backbone
with phosphorothioate at 5' and 3' ends

<400> 757
tctcccagcg tgcgccatat 20

<210> 758
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<221> misc_feature
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with phosphorothioate at 5' and 3' ends

<400> 758
tctcccagcg tgcgcctttt 20

<210> 759
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<221> misc_feature
<222> (0)...(0)
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<400> 759
tctcccagcg tgcgtgcgcc at 22

<210> 760
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with phosphorothioate at 5' and 3' ends

<400> 760
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<210> 761
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<221> misc_feature
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<400> 761
tctcccagcg tgcgtttt 18

<210> 762
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with phosphorothioate at 5' and 3' ends

<400> 762
tctcccagcg ttgcgccata t 21

<210> 763
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<220>
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<221> misc_feature
<222> (0)...(0)
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<400> 763
tctcccatcg tcgccat 17

<210> 764
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<221> misc_feature
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<400> 764
tctcccgacg tgcgccat 18

<210> 765
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<221> misc_feature
<222> (0)...(0)
<223> phosphorothioate backbone

<400> 765
tctcccgtcg tgcgccat 18

<210> 766
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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphorothioate at 5' and 3' ends

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with phosphodiester on 3' end

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<221> modified_base
<222> (2)...(2)
<223> m5c

<400> 844
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<221> modified_base
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<223> m5c

<400> 846
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<221> modified_base
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<223> m5c

<221> modified_base
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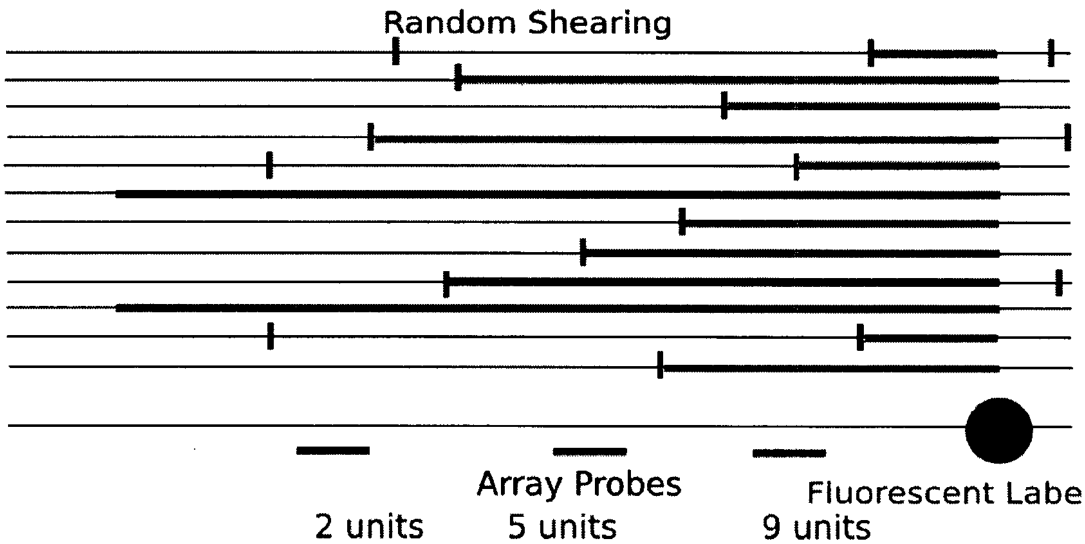


Figure 1: The ruler array relies on probabilistic breaking of genomic DNA such that as the two ends of the ruler move farther apart in the genome, the probability of a DNA fragment containing both ends decreases. Imagine fixing a label to some point in the genome and the randomly fragmenting many copies of that genome. When the resulting material hybridizes to a microarray, probes near the labeled site will show higher intensities than probes farther away because fewer breaks occur over a short distance than a long one. The fraction of the genome interrogated by this method depends on the distribution of labeled sites throughout the genome, the length of DNA fragments, and the presense of microarray probes in the genome.

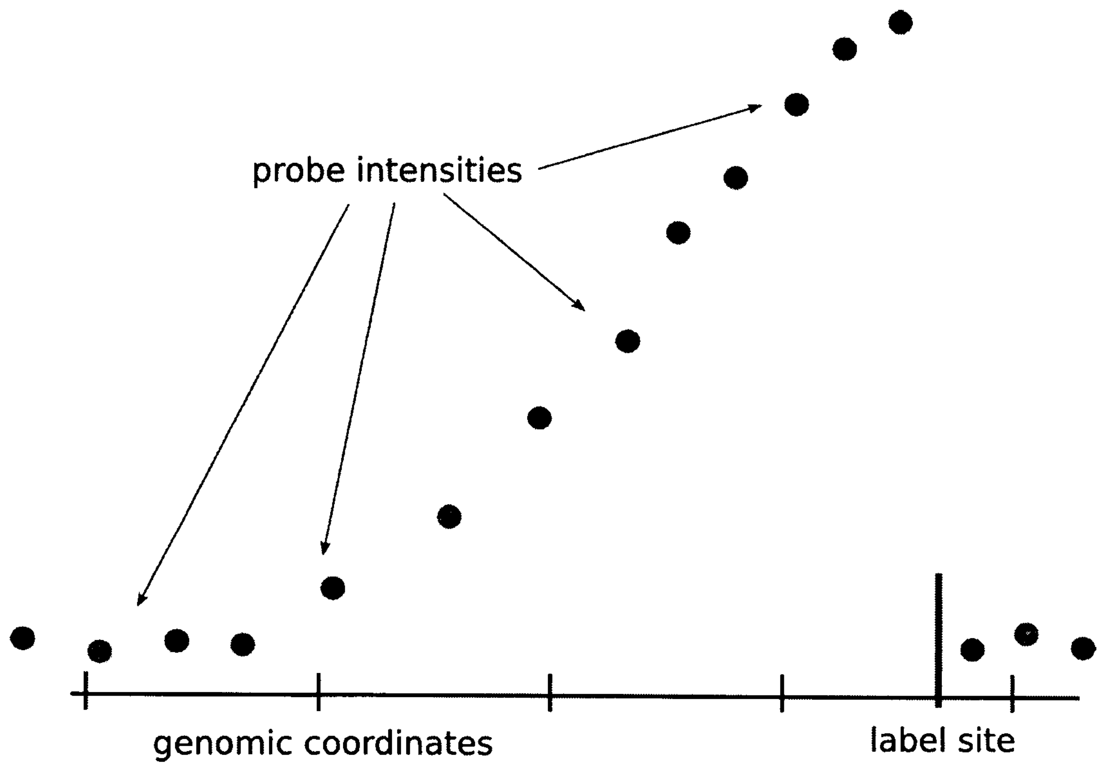


Figure 2: Array probes complementary to the material produced by the labeled site will show high intensity close to the site and lower intensity at longer distances. At some distance, the observed probe intensities will fall to a background level; the maximum length of DNA fragments and the limitations of the labeling technique determine this distance.

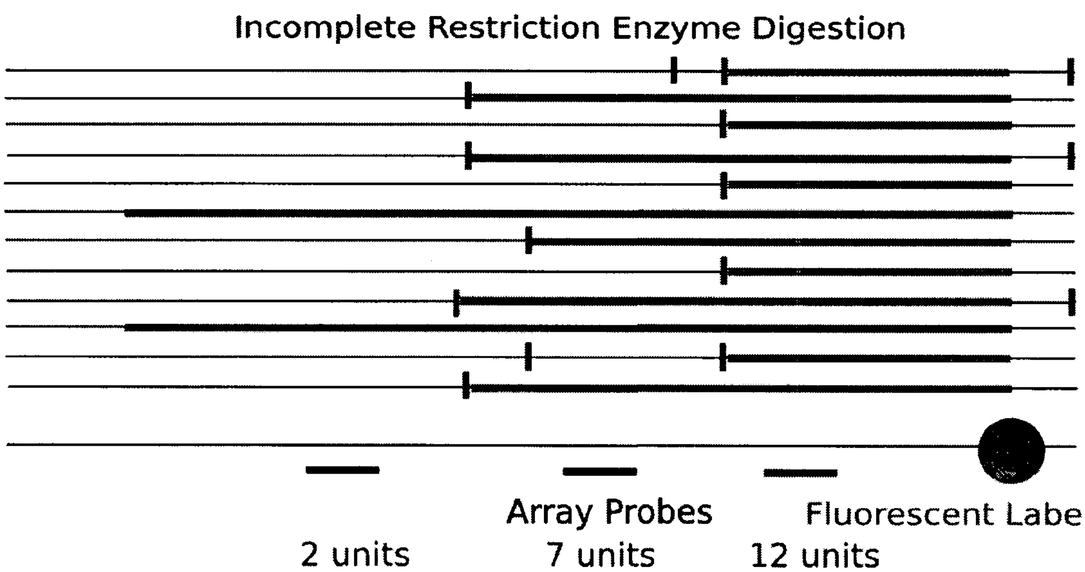


Figure 3: Several methods could suitably break the genomic DNA. While sonication or pipetting would break the DNA pseudorandomly, incomplete restriction enzyme digestion would probabilistically cut the DNA at certain locations.

Digest	AGTGGGACGTGGACAGAATTC TCACCCTGCACCTGTCTTAAG
Add Oligo Pair	AGTGGGACGTGGACAG TCACCCTGCACCTGTCTTAA AATTGGAGGAGGGAAGGGGG CCTCCTCCCTTCCCCC
Ligate	AGTGGGACGTGGACAGAATTGGAGGAGGGAAGGGGG TCACCCTGCACCTGTCTTAA
Add Oligo	AGTGGGACGTGGACAGAATTGGAGGAGGGAAGGGGG CCTCCTCCCTTCCCCC
PCR Extend	AGTGGGACGTGGACAGAATTGGAGGAGGGAAGGGGG TCACCCTGCACCTGTCTTAACCTCCTCCCTTCCCCC

Figure 4: Digest-Ligate-Sonicate-Label-Hybridize. We first digest the genomic DNA with one or several restriction enzymes that leave sticky ends. We then add adapter oligos that contain (1) a 5' sequence complementary to the sticky end and (2) an arbitrary 3' end chosen for our convenience. We use a partially double-stranded oligo pair such that part (1) is single stranded and part (2) is double stranded. After the ligation, the longer adapter molecule is firmly attached to the genomic DNA while the shorter primer oligo may disassociate. We then add more of the shorter oligo to prime a PCR extension to incorporate labeled nucleotides. This primer will hybridize to, and thus prime, the adapter molecule ligated onto the restriction enzyme sites as well as any genomic loci to which it is complementary. While this figure shows the labeling of genomic DNA on one side of the restriction site, the reaction will actually label in both directions on opposite strands.

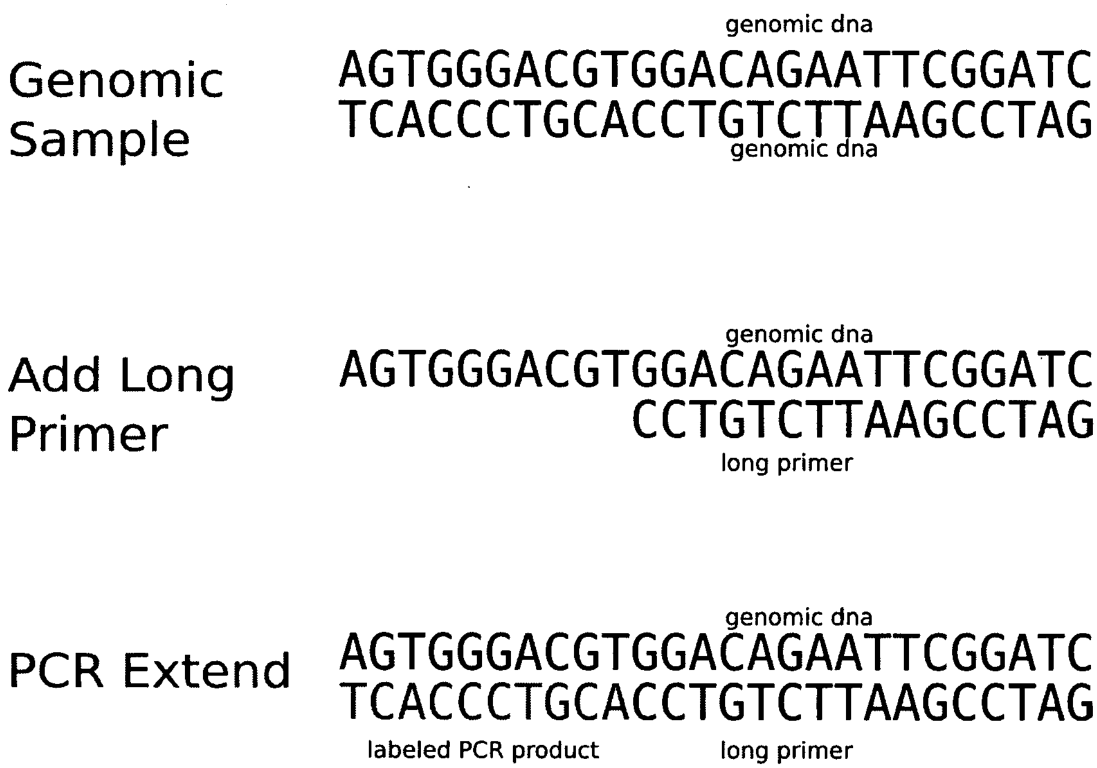


Figure 5: This labeling technique uses one or more oligos directly against genomic DNA (without the digestion and ligation steps). By using a relatively long oligo, the amplification targets specific genomic loci. While this may provide data over a relatively small fraction of a genome, it makes insertions or deletions of the labeled site extremely obvious. This technique would be useful if the oligo or oligos label sites contained in transposable elements or other sequences suspected of changing between two genomic samples.

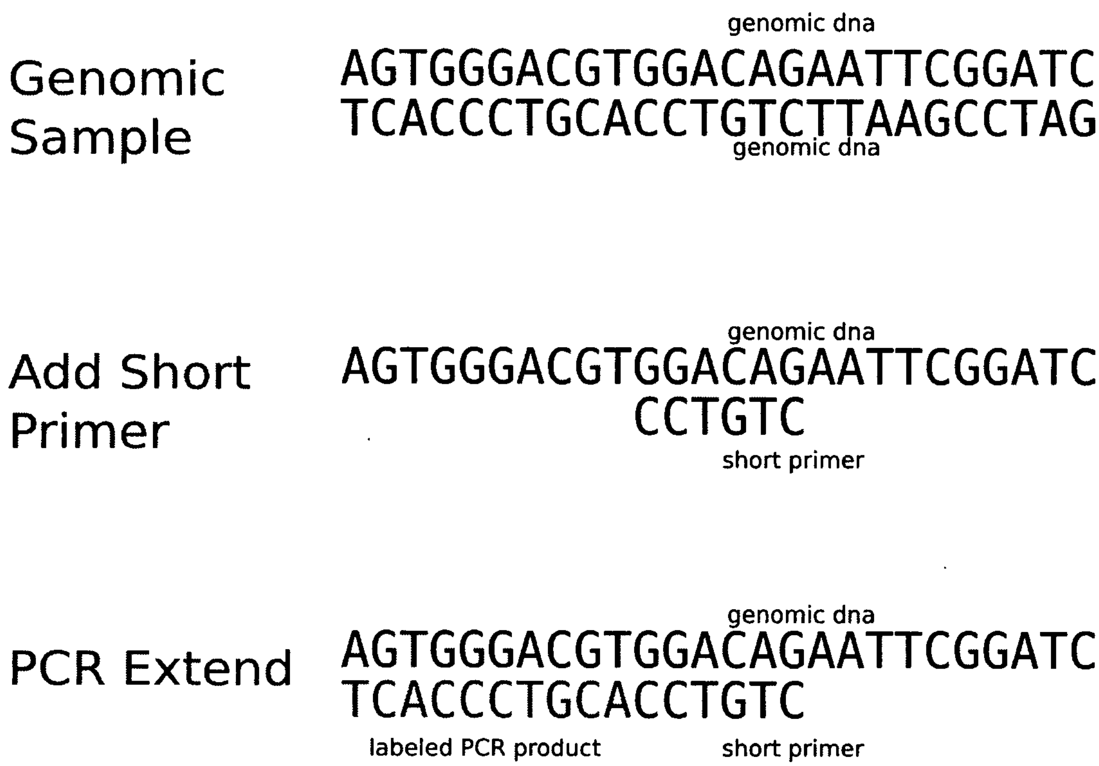


Figure 6: Using short sequences to prime a PCR reaction that incorporates labeled nucleotides is similar to the long oligos but will label more genomic locations. Using hexamers, for example, should label roughly as many sites as a restriction enzyme that recognizes a six nucleotide sequence, but the hexamer offers more flexibility. In particular, we might choose a hexamer whose genomic locations are more uniformly distributed through the genome than any available restriction site, thus providing data about a larger fraction of that genome.

Figure 7: This variation on the Digest/Ligate protocol uses an oligo into which dye has been incorporated prior to the ligation. Pre-labeling the oligo removes the need for the PCR step and has the added advantage of incorporating the same amount of dye at each restriction site.

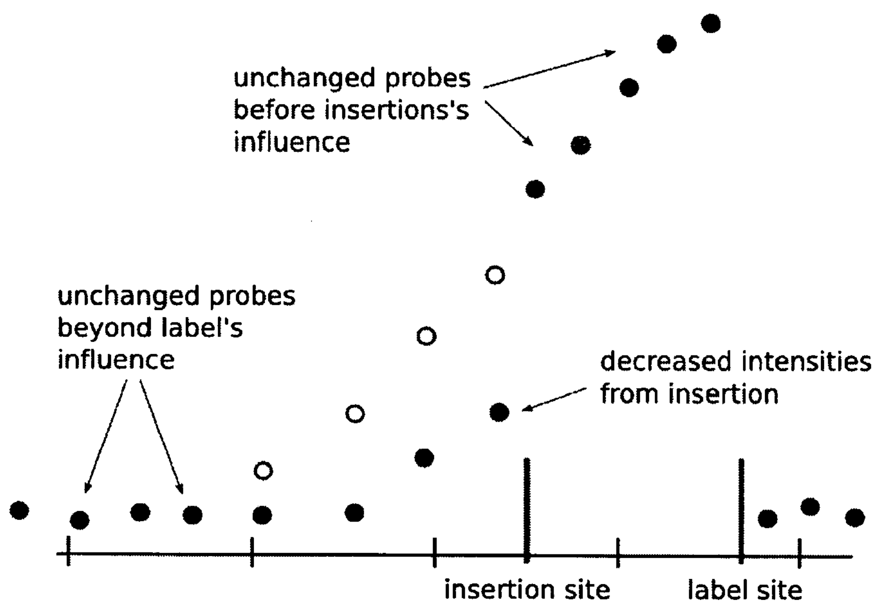


Figure 8: When the distance between a probe and a labeling site increases compared to the expected distance, the probes will observe lower intensities than expected. We can determine the location of an insertion by observing a more rapid decrease in intensity than the expected distances alone would predict.

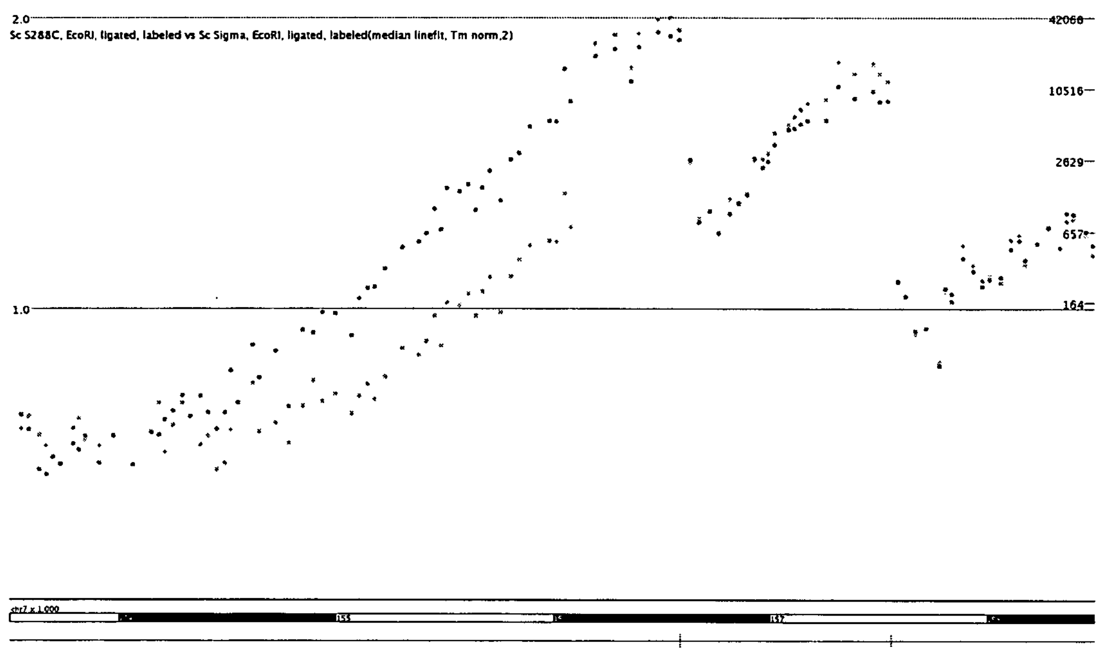


Figure 9: This plot shows ruler data from two strains of *Saccharomyces cerevisiae* generated using the Digest/Ligate/Sonicate protocol. The red dots show intensities from $\Sigma 1278B$ and the green dots denote intensities from $S288C$. The red tick marks at the bottom show EcoRI digest sites and the black and white bars each represent 1,000bp. The intensities in the two channels are very similar close to the EcoRI site. The Σ intensities drop off gradually (the slope extends only in one direction because this microarray only included probes on one strand. An array with probes on both strands would show a symmetric shape) while the $S288C$ intensities drop rapidly at one point. This rapid drop indicates an insertion in $S288C$ relative to Σ. An analysis method would detect this sudden change in slope to recognize the insertion.

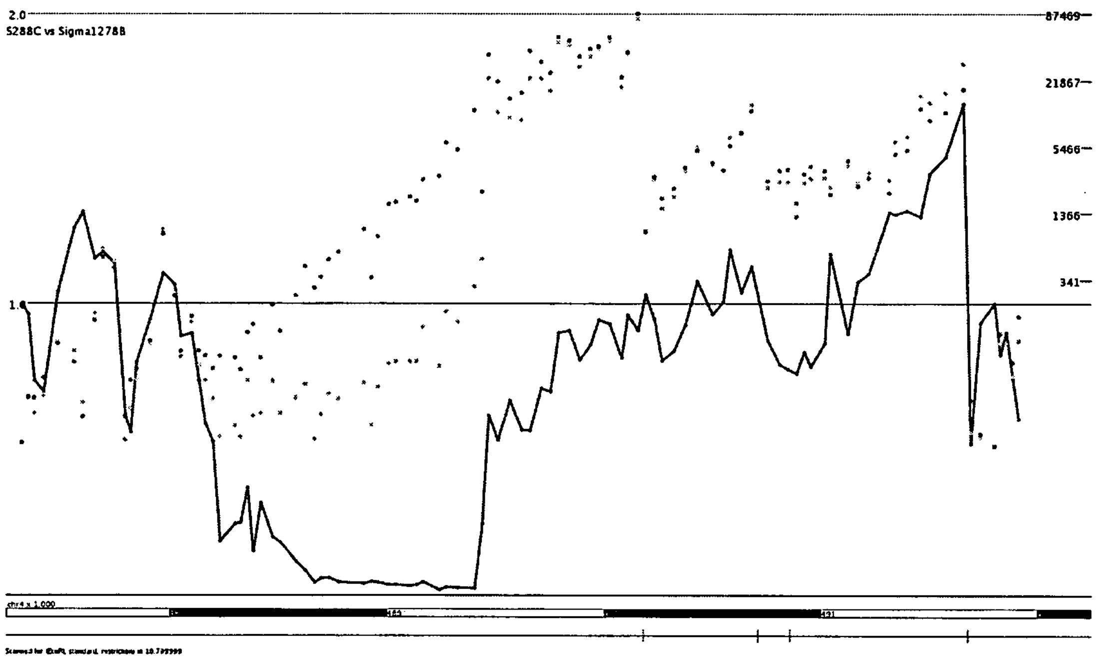


Figure 10: In this example of an insertion between two yeast strains, the blue line shows the ratio of the intensities at each probe. The sudden drop in ratio from roughly one to a much smaller value (it would be a sudden increase if the channels were swapped) indicates the presense of an insertion. The ratio remains low to the edge of the probes influenced by the restriction site and then returns to roughly one as both the probe observes only background noise in both channels.

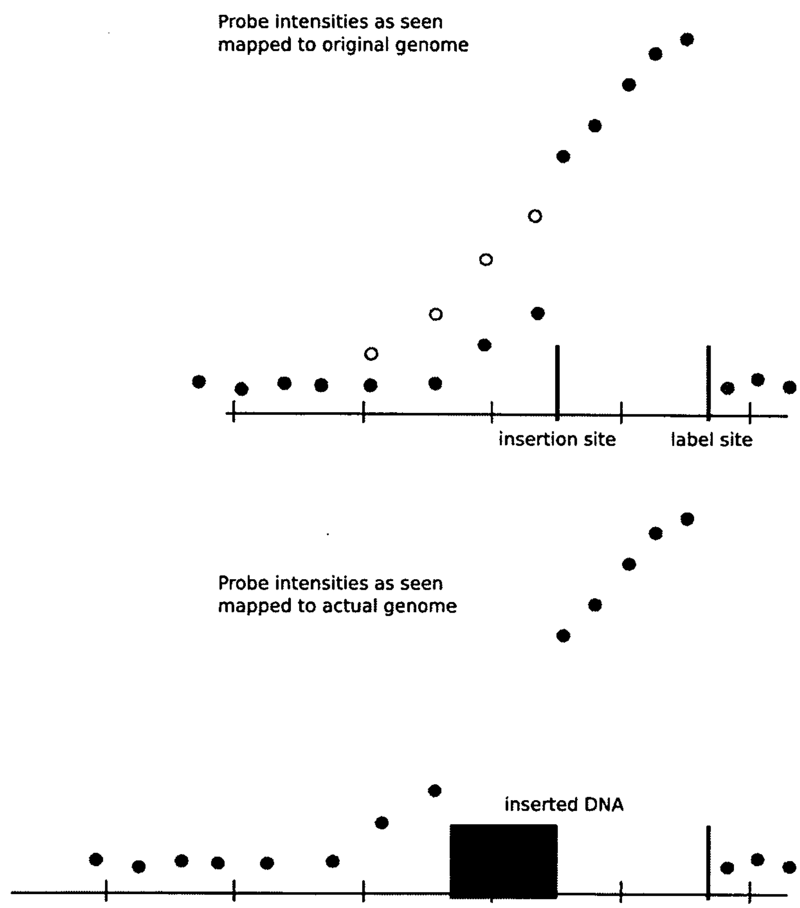


Figure 11: We can estimate the site of the insertion as the amount of DNA that best matches the observed decrease in probe intensity

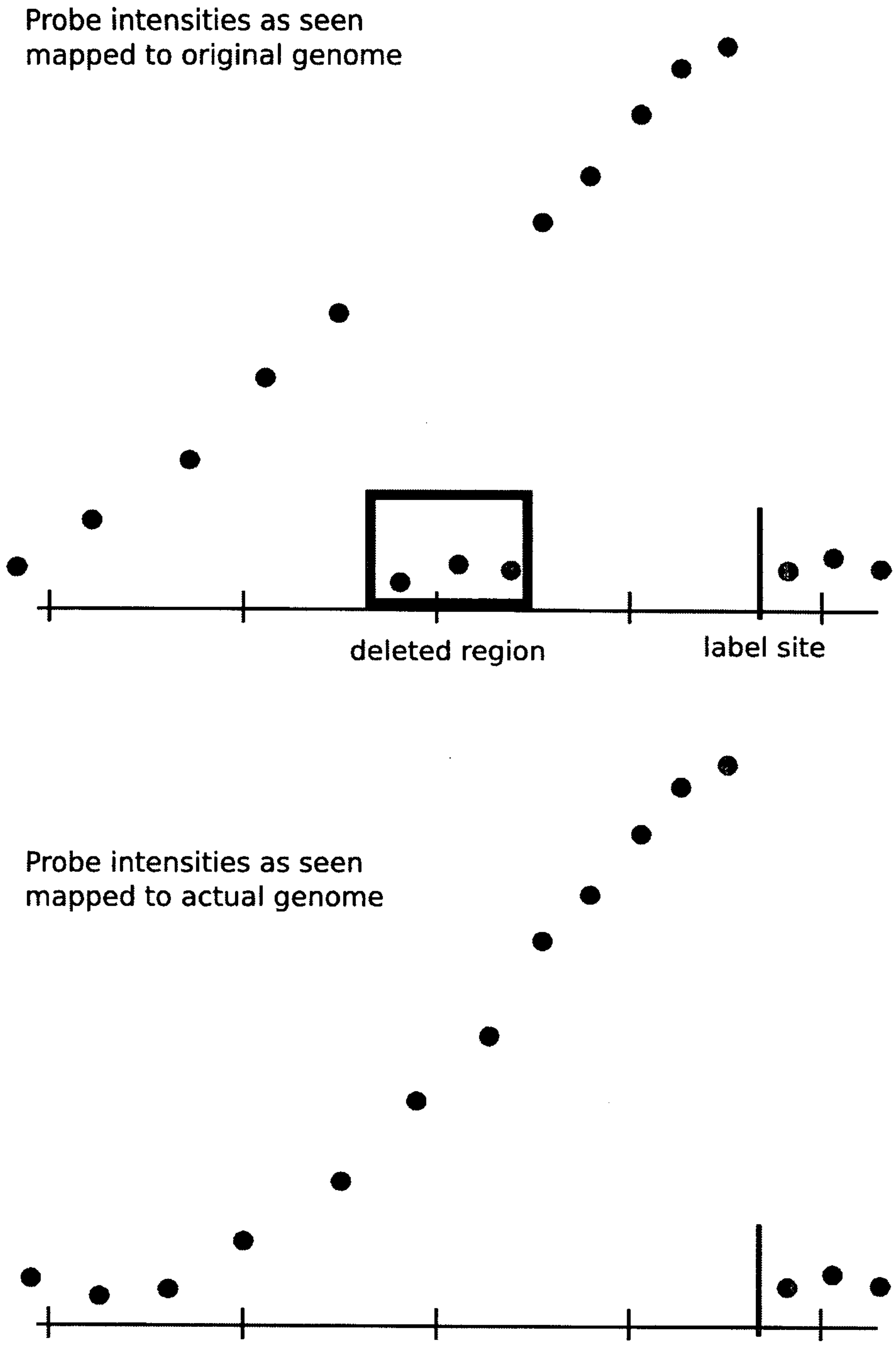


Figure 12: Large deletions will cause some probes to yield extremely low values as the genomic sequence complementary to the probe is not present in the sample. Probes farther from the label site than the deletion will produce higher than expected intensities. Small deletions may not delete any probes from the genome, but will still produce higher than expected intensities at probes beyond the insertion.

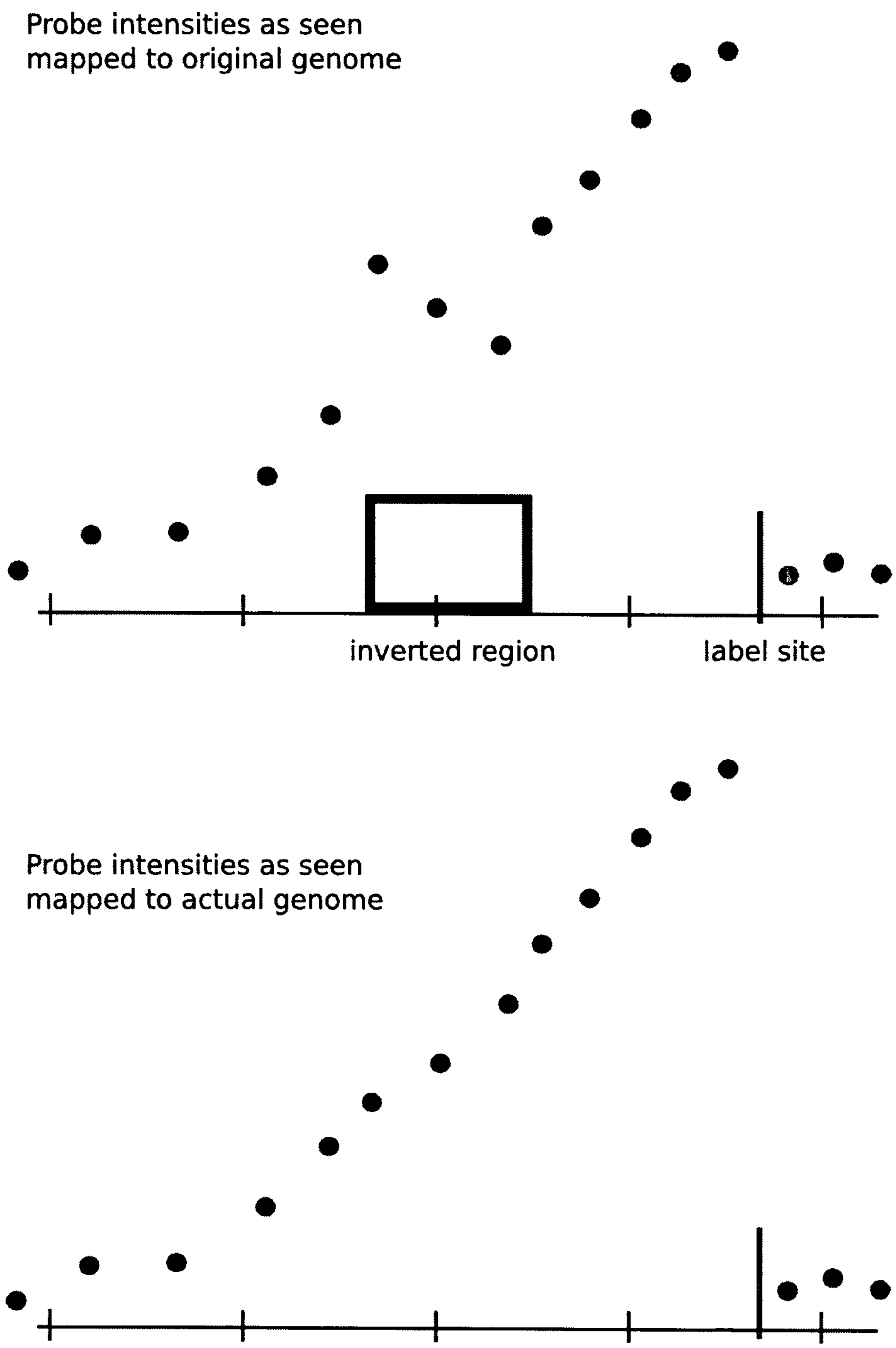


Figure 13: An inverted segment of DNA should also be observable because the pattern of observed probe intensities will not match the expected pattern.

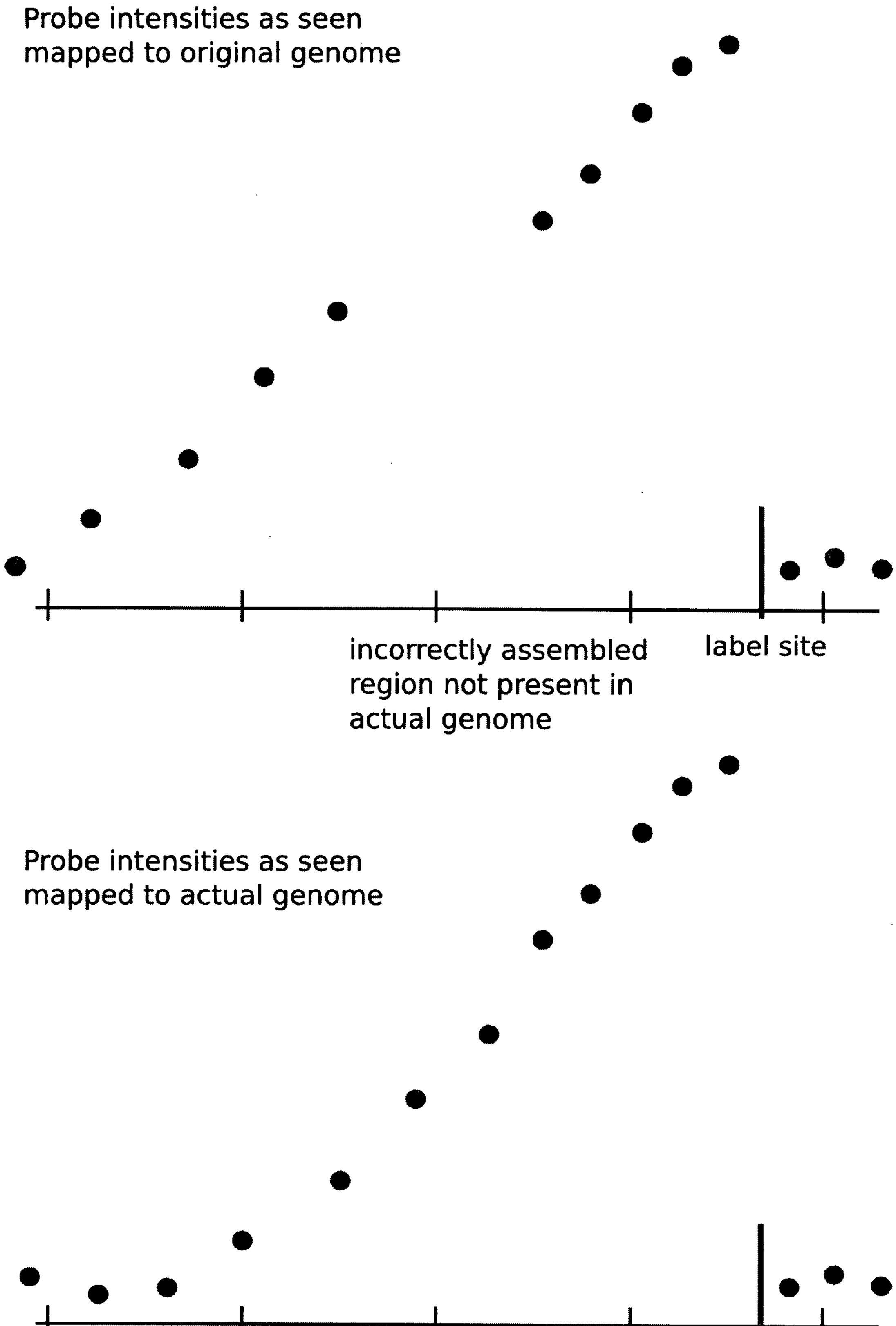


Figure 14: Assembly programs that turn paired-end reads into scaffolds and chromosomes rely on prior knowledge about the distance between the two paired ends. If that expectation about the distance between the two reads is wrong, it may lead to assembly errors. This example shows how an assembler might erroneously insert space (typically shown in the assembly output as a long string of Ns) not actually present in the genome.

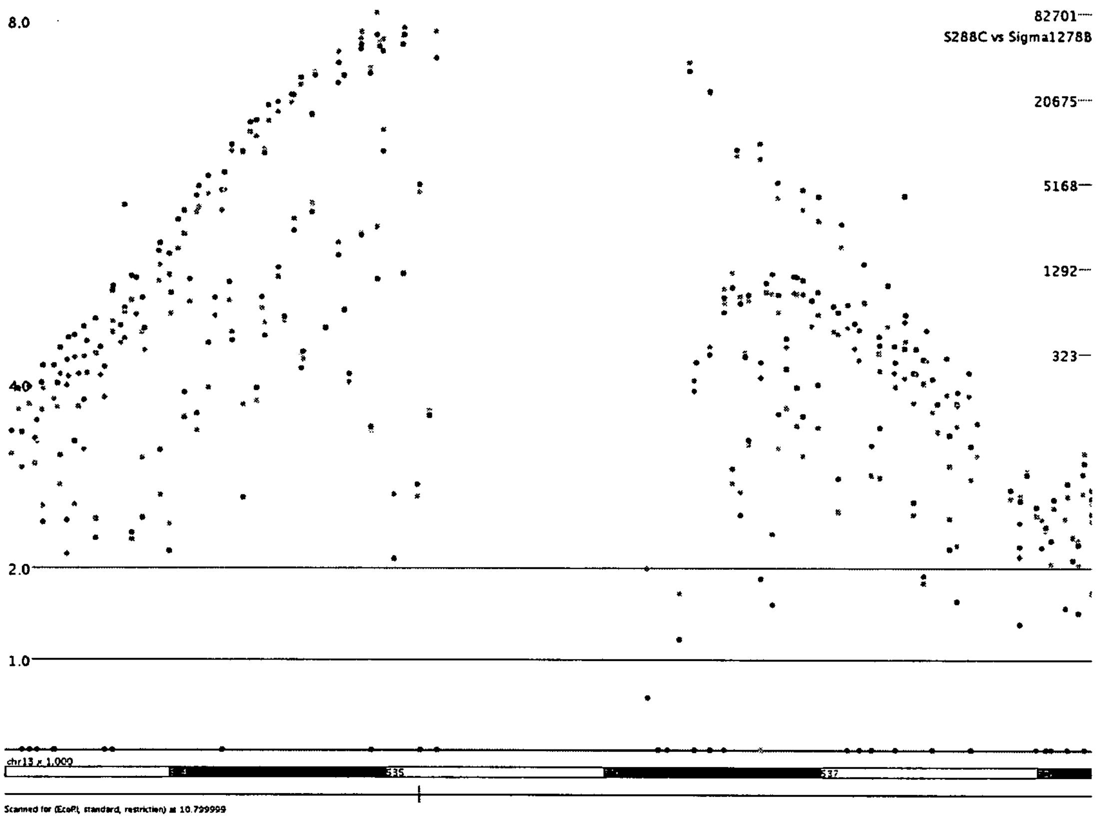
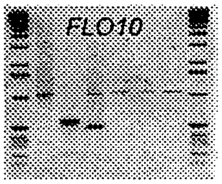


Figure 15: This example shows data from $S288C$ and $\Sigma1278B$. The microarray included probes from both strands producing the symmetric peaks. The gap in the probes (just to the right of the EcoRI site) is an assembly artifact. If that region were not present, the intensities in both channels would fall off smoothly indicating that the probes to the right of the gap are in fact close to the EcoRI site rather than the 1kb away that the genome assembly suggests.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